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Sieve maximum likelihood regression analysis of dependent current status data

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SUMMARY

Current status data occur in contexts including demographic studies and tumorigenicity experiments. In such cases, each subject is observed only once and the failure time of interest is either left- or right-censored (Kalbfleisch & Prentice, 2002). Many methods have been developed for the analysis of such data (Huang, 1996; Sun, 2006), most of which assume that the failure time and the observation time are independent completely or given covariates. In this paper, we present a sieve maximum likelihood approach for current status data when independence does not hold. A copula model and monotone I-splines are used and the asymptotic properties of the resulting estimators are established. In particular, the estimated regression parameters are shown to be semiparametrically efficient. An illustrative example is provided.

Some key words: Copula model; Current status data; I-spline; Informative censoring; Proportional hazards model.

1. INTRODUCTION

Many authors have discussed the analysis of current status data (Andersen & Ronn, 1995; Chen et al., 2009; Finkelstein & Schoenfeld, 1989; Huang, 1996; Jewell & van der Laan, 1996; Lin et al., 1998; Rossini & Tsiatis, 1996; Sun, 1999). For example, Huang (1996), Rossini & Tsiatis (1996), and Lin et al. (1998) investigated regression analysis of current status data under the proportional hazards model, proportional odds model, and additive hazards model, respectively. However, most existing methods assume that the failure time of interest and the observation time are independent completely or given covariates. This assumption may not hold, and the resulting data are often referred to as dependent or informative current status data.

One well-known example of dependent current status data arises from tumorigenicity experiments, in which the failure time of interest is usually the time to tumor onset. One usually observes only current status data because the presence or absence of tumors can be determined only at the animal death. As most tumors are between lethal and nonlethal, this implies that the tumor and death times can be related and thus we observe dependent current status data. There has been a lot of work on dependent current status data, but most approaches are parametric (Dewanji & Kalbfleisch, 1986; Lagakos & Louis, 1988).

Several semiparametric methods have been proposed. For example, Zhang et al. (2005) considered regression analysis under the additive hazards model and Chen et al. (2012) investigated the same problem under the linear transformation model. Both used latent variables to characterize the correlation between the failure time of interest and the observation time. However, the methods apply only to the limited situations specified by the assumed structure on the latent variables, and no rigorous theoretical justification was provided. In this paper, we employ a copula approach, which applies to much more general situations, to model the failure and observation times jointly.

2. NOTATION, MODELS AND LIKELIHOOD FUNCTION

Consider a failure time study that involves n independent subjects and in which each subject is observed only once. For subject i, let T_i denote the failure time of interest, C_i the potential observation time which may depend on T_i, and Z_i a p-dimensional vector of covariates, where $i = 1, \ldots, n$. Suppose that there also exists a censoring time ζ_i such as the administrative stop time. In the case of tumorigenicity experiments, for example, T_i, C_i, and ζ_i represent the times to tumor onset, animal death, and sacrifice or study end, respectively. Define $\tilde{C}_i = \min(C_i, \zeta_i)$, $\Delta_i = I(C_i \leqslant \zeta_i)$, and $\delta_i = I(T_i \leqslant \tilde{C}_i)$. Then the observed data have the form $\{X_i = (\Delta_i, \delta_i, \tilde{C}_i, Z_i), i = 1, \ldots, n\}$.

To describe the effects of covariates, in the following, we assume that given Z_i, T_i and C_i follow the marginal proportional hazards models given by

$$\lambda^{(T)}(t \mid Z_i) = \lambda_1(t) \exp(Z_i^{\mathrm{T}}\beta) \tag{1}$$

and

$$\lambda^{(C)}(c \mid Z_i) = \lambda_2(c) \exp(Z_i^{\mathrm{T}}\gamma),$$

respectively. Here $\lambda_1(t)$ and $\lambda_2(c)$ denote unknown baseline hazard functions and β and γ are p-dimensional vectors of regression parameters. Let F_T and F_C denote the marginal distributions of T_i and C_i, respectively, and F the joint distribution of T_i and C_i. Then there exists a copula function $C_\alpha(u, v)$ defined on $I^2 = [0, 1] \times [0, 1]$ such that (Nelsen, 2006),

$$F(t, c) = C_\alpha\{F_T(t), F_C(c)\}. \tag{2}$$

Here α is often referred to as the association parameter representing the relationship between T_i and C_i, and $C_\alpha(u, 0) = C_\alpha(0, v) = 0$, $C_\alpha(u, 1) = u$ and $C_\alpha(1, v) = v$. Then

$$\mathrm{pr}(T \leqslant t \mid C = c, Z_i) = \left.\frac{\partial C_\alpha(u, v)}{\partial v}\right|_{u=F_T(t), v=F_C(c)} = m_\alpha\{F_T(t), F_C(c)\}$$

and the resulting likelihood function has the form

$$L(\theta) = \prod_{i=1}^{n} \left\{ \left([m_\alpha\{F_T(\tilde{c}_i), F_C(\tilde{c}_i)\}]^{\delta_i} [1 - m_\alpha\{F_T(\tilde{c}_i), F_C(\tilde{c}_i)\}]^{1-\delta_i} f_C(\tilde{c}_i) \right)^{\Delta_i} \right.$$
$$\left. \times \left([F_T(\tilde{c}_i) - C_\alpha\{F_T(\tilde{c}_i), F_C(\tilde{c}_i)\}]^{\delta_i} [1 - F_T(\tilde{c}_i) - F_C(\tilde{c}_i) + C_\alpha\{F_T(\tilde{c}_i), F_C(\tilde{c}_i)\}]^{1-\delta_i} \right)^{1-\Delta_i} \right\},$$

with f_C denoting the marginal density function of C_i and $\theta = \{\beta^{\mathrm{T}}, \gamma^{\mathrm{T}}, \Lambda_T(\cdot), \Lambda_C(\cdot)\}^{\mathrm{T}}$, where $\Lambda_T(t) = \int_0^t \lambda_1(s)\,\mathrm{d}s$ and $\Lambda_C(c) = \int_0^c \lambda_2(s)\,\mathrm{d}s$.

The formulation (2) or of the copula approach is commonly used in multivariate failure time data analysis. It has also been applied to univariate failure time data in the presence of informative censoring. For example, Zheng & Klein (1995) and Chen (2010) investigated the estimation of a survival function and regression analysis based on right-censored data in the presence of dependent competing risks. Wang et al. (2012) and Titman (2014) studied nonparametric estimation of a survival function based on dependent current status data and showed that without prior or extra information, the association parameter α is not

identifiable given a specified parametric family of copulas. Following these authors, we will assume that both the copula function and α are known and our main goal is to estimate the regression parameters β and γ.

3. Sieve semiparametric maximum likelihood estimation

Now we discuss the estimation of the parameters θ. A natural approach is to maximize the loglikelihood function $l(\theta) = \log L(\theta)$, but this is difficult due to the dimensions of $\Lambda_T(\cdot)$ and $\Lambda_C(\cdot)$. To address this, following Huang & Rossini (1997) and others, we consider the sieve maximum likelihood approach by approximating $\Lambda_T(\cdot)$ and $\Lambda_C(\cdot)$ with I-spline functions (Lu et al., 2007; Ramsay, 1988).

More specifically, let M denote a positive constant and $\{I_j(t)\}_{j=1}^{m+k_n}$ the I-spline base functions with order m and k_n interior knots, where $k_n = o(n^\nu)$ with $0 < \nu < 0{\cdot}5$. The selection of m and k_n will be discussed below. Let $\varphi = (\Lambda_T, \Lambda_C)$ and define

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

where $\mathcal{B} = \{(\beta, \gamma) \in R^{2p}, \|\beta\| + \|\gamma\| \leqslant M\}$ with $\|v\|$ defined as the Euclidean norm for a vector v, $\mathcal{M}_n^1 = \{\Lambda_{Tn} : \Lambda_{Tn}(t) = \sum_{j=1}^{m+k_n} \xi_j I_j(t), \xi_j \geqslant 0, j = 1, \ldots, m + k_n, t \in [0, u_c]\}$ and $\mathcal{M}_n^2 = \{\Lambda_{Cn} : \Lambda_{Cn}(t) = \sum_{j=1}^{m+k_n} \eta_j I_j(t), \eta_j \geqslant 0, j = 1, \ldots, m + k_n, t \in [0, u_c]\}$ with u_c being the upper bound of all observation times $\{\tilde{C}_i : i = 1, \ldots, n\}$. We use the same I-spline base functions as well as the same degree and interior knot numbers for Λ_{Tn} and Λ_{Cn}, because we observe only the $\tilde{C}_i$.

It follows from Lemma A1 of Lu et al. (2007) that Θ_n can be used as a sieve space of Θ. For estimation of θ, we define the estimator $\hat{\theta} = \{\hat{\beta}^{\mathrm{T}}, \hat{\gamma}^{\mathrm{T}}, \hat{\Lambda}_{Tn}(\cdot), \hat{\Lambda}_{Cn}(\cdot)\}^{\mathrm{T}}$ as the value of θ that maximizes the loglikelihood function $l(\theta)$ over Θ_n. Let $\theta_0 = (\beta_0^{\mathrm{T}}, \gamma_0^{\mathrm{T}}, \Lambda_{T0}, \Lambda_{C0})^{\mathrm{T}}$ denote the true values of θ. For the asymptotic properties of $\hat{\theta}$, we need the following regularity conditions.

Condition 1. The covariate Z has a bounded support in R^p.

Condition 2. The copula function $C(\cdot, \cdot)$ has bounded first-order partial derivatives with $\partial C(u, v)/\partial u$ and $\partial C(u, v)/\partial v$ being Lipschitz.

Condition 3. (i) If there exist constants c_0 and $\tilde{\gamma}$ such that $\tilde{\gamma}^\tau Z = c_0$ almost surely, then $c_0 = 0$, $\tilde{\gamma} = 0$. (ii) Assume that $\mu_C(E) > 0$ for any open set $E \in I^2$, where μ_C denotes the probability measure corresponding to the copula function C given Z.

Condition 4. For some $\eta \in (0, 1]$, the functions $\Lambda_T(\cdot)$ and $\Lambda_C(\cdot)$ belong to

$$\mathcal{A} = \{\Lambda(\cdot); |\Lambda^{(\kappa)}(t_1) - \Lambda^{(\kappa)}(t_2)| \leqslant M|t_1 - t_2|^\eta, t_1, t_2 \in (l, u)\},$$

where $\Lambda_T^{(\kappa)}(\cdot)$ and $\Lambda_C^{(\kappa)}(\cdot)$ denote the κth derivatives of $\Lambda_T(\cdot)$ and $\Lambda_C(\cdot)$, respectively, and M and (l, u) are some constants. Define $r = \kappa + \eta$.

Condition 5. The matrix $E(S_\vartheta S_\vartheta^{\mathrm{T}})$ is finite and positive definite, where $\vartheta = (\beta^{\mathrm{T}}, \gamma^{\mathrm{T}})^{\mathrm{T}}$ and S_ϑ is defined in the proof of Theorem 3 in the Supplementary Material.

The conditions above are generally mild and satisfied in practical situations (Huang & Rossini, 1997; Zhang et al., 2010). Condition 3 is needed for the identifiability of the parameters. In particular, Condition 3 (i) is equivalent to the linear independence of Z and similar conditions to Condition 3 (ii) are also used in Zheng & Klein (1995). Now we describe the asymptotic properties of $\hat{\theta}$.

Theorem 1. *Assume that Conditions* 1–3 *hold. Then* $\hat{\beta}$ *and* $\hat{\gamma}$ *are strongly consistent, and*

$$\|\hat{\Lambda}_{Tn} - \Lambda_{T0}\|_2 \to 0, \quad \|\hat{\Lambda}_{Cn} - \Lambda_{C0}\|_2 \to 0$$

almost surely as $n \to \infty$, *where* $\|g(Y)\|_2 = (\int |g|^2 \, dP)^{1/2}$ *is defined as the* $L_2(P)$ *norm for a function* g *with* P *being the probability measure for* Y.

THEOREM 2. *Assume that Conditions* 1–4 *hold. Then as* $n \to \infty$, *we have*

$$\|\hat{\Lambda}_{Tn} - \Lambda_{T0}\|_2 + \|\hat{\Lambda}_{Cn} - \Lambda_{C0}\|_2 = O_p(n^{-(1-v)/2} + n^{-rv}),$$

where r *is defined in Condition* 4.

THEOREM 3. *Suppose that Conditions* 1–5 *hold and* $r > 2$ *in Condition* 4. *Then as* $n \to \infty$, *we have*

$$n^{1/2}\left\{(\hat{\beta} - \beta_0)^{\mathrm{T}}, (\hat{\gamma} - \gamma_0)^{\mathrm{T}}\right\}^{\mathrm{T}} \to N(0, \Sigma)$$

in distribution, where Σ *is defined in the Supplementary Material, and furthermore,* $(\hat{\beta}^{\mathrm{T}}, \hat{\gamma}^{\mathrm{T}})^{\mathrm{T}}$ *is semiparametrically efficient.*

To implement the sieve maximum likelihood estimation procedure, one needs to choose m and k_n. In general, the degree m should be decided by the smoothness of the true baseline cumulative hazard functions, and either quadratic or cubic spline functions usually work sufficiently well. Of course, one could try different values of them and compare the obtained results. As an alternative, one can apply the AIC to choose m and k_n that give the smallest AIC. Given m and k_n, the computation of $\hat{\theta}$ is relatively easy, as one can employ software such as the R (R Development Core Team, 2015) function nlm. One must impose nonnegativity constraints on the I-spline coefficients or one can use a logarithmic transformation of the coefficients before applying nlm. In the method developed in this section, it has been assumed that both the copula function $C_\alpha(\cdot, \cdot)$ and the association parameter α are known without prior or extra information. In practice, one could also use the AIC to select them; see also § 5.

To implement the proposed estimation procedure, one needs to estimate the covariance matrix of $\hat{\beta}$ and $\hat{\gamma}$ or Σ. The profile likelihood approach may be difficult to apply. A simple alternative, which will be used below in numerical studies, is to employ the inverse observed information matrix by treating Λ_{Tn} and Λ_{Cn} as finite-dimensional nuisance parameters (Huang et al. , 2012). The simulation results below suggest that this works well in practice.

4. SIMULATION STUDIES

An extensive simulation study was performed to evaluate our estimation procedure. We assumed that there are two covariates, $Z = (Z_1, Z_2)^{\mathrm{T}}$, where Z_1 follows the Bernoulli distribution with success probability 0·5 and Z_2 follows the uniform distribution over (0, 1). Consider the following copula models:

$$C_\alpha(u, v) = \exp\left[-\{(-\log u)^\alpha + (-\log v)^\alpha\}^{1/\alpha}\right], \quad \alpha \geqslant 1, \tag{3}$$

$$C_\alpha(u, v) = uv + \alpha uv(1-u)(1-v), \quad -1 \leqslant \alpha \leqslant 1, \tag{4}$$

$$C_\alpha(u, v) = \log_\alpha\left\{1 + \frac{(\alpha^u - 1)(\alpha^v - 1)}{\alpha - 1}\right\}, \quad \alpha \geqslant 0, \alpha \neq 1, \tag{5}$$

usually referred to as Gumbel, Farlie–Gumbel–Morgenstern, and Frank models, respectively. The range of the association parameter α is different in the three copula families. In the following, we use Kendall's τ as a global measure of association between the failure time T_i and the observation time C_i. For model (3), $\tau = 1 - 1/\alpha$, and $\tau = 2\alpha/9$ for model (4). Under model (5), the relationship is $\tau = 1 + 4\rho^{-1}\{D_1(\rho) - 1\}$, where $\rho = -\log\alpha$ and $D_1(\rho) = \rho^{-1}\int_0^\rho t(e^t - 1)^{-1}\,\mathrm{d}t$. To generate the observed data, we first generated the failure time T_i under the proportional hazards model (1) with $\Lambda_{T0}(t) = t$. Then we generated the observation times C_i from their conditional distribution given T_i with $\Lambda_{C0}(c) = 0{\cdot}5c$. More specifically, given $T_i = t_i$ and a random number a generated from the uniform distribution over (0, 1), we solve the equation

$$\mathrm{pr}(C \leqslant c_i \mid T = t_i, Z) = \left.\frac{\partial C_\alpha(u, v)}{\partial u}\right|_{u=F_T(t_i), v=F_C(c_i)} = a$$

Table 1. *Simulation results on estimation of regression parameters with correctly specified and misspecified copula models and* τ

	True	Bias $\times 10^2$	SSE $\times 10^2$	SEE $\times 10^2$	CP $\times 10^2$	Bias $\times 10^2$	SSE $\times 10^2$	SEE $\times 10^2$	CP $\times 10^2$
		Part I: Data generated from model (5) with $\tau = 0{\cdot}5$							
		Analysis assuming model (5) with $\tau = 0{\cdot}5$				Analysis assuming model (5) with $\tau = 0$			
β_1	0·5	1	22	21	93	−25	22	21	73
β_2	0·5	0	37	35	93	−24	41	37	87
γ_1	0·5	0	16	15	95	0	161	16	95
γ_2	0·5	−1	26	26	95	0	26	27	96
		Part II: Data generated from model (5) with $\tau = 0{\cdot}5$							
		Analysis assuming model (5) with $\tau = -0{\cdot}2$				Analysis assuming model (5) with $\tau = 0{\cdot}2$			
β_1	0·5	−36	21	20	53	−13	23	22	88
β_2	0·5	−36	40	35	79	−13	41	37	92
γ_1	0·5	0	16	16	95	0	16	15	95
γ_2	0·5	0	26	27	96	0	26	27	96
		Part III: Data generated from model (3) with $\tau = 0{\cdot}5$							
		Analysis assuming model (5) with $\tau = 0{\cdot}5$				Analysis assuming model (5) with $\tau = 0$			
β_1	0·5	12	24	23	92	−13	25	24	90
β_2	0·5	11	41	39	94	−14	44	41	92
γ_1	0·5	0	16	15	95	0	16	15	95
γ_2	0·5	−1	26	26	96	0	26	27	96
		Part IV: Data generated from model (4) with $\tau = 0{\cdot}1$							
		Analysis assuming model (5) with $\tau = 0{\cdot}1$				Analysis assuming model (5) with $\tau = 0$			
β_1	0	0	24	22	95	−9	25	23	92
β_2	0·5	1	41	40	95	−13	42	41	95
γ_1	0·5	1	16	15	95	1	16	15	95
γ_2	1	0	27	27	95	0	27	27	95

True, true value of regression parameter; Bias, mean of the estimates minus the true value; SSE, sample standard deviation of the estimates; SEE, mean of estimated standard errors; CP, 95% empirical coverage probability.

for $C_i = c_i$. The constant censoring times $\zeta_i = \zeta$ were used in all results. For the approximation of Λ_{T0} and Λ_{C0}, we employed quadratic splines using the 0·2, 0·4, 0·6, 0·8 quantiles of the $\tilde{C}_i$ as four interior knots. The results below are based on 500 replications and $n = 200$.

Table 1 presents some results on estimation of regression parameters. Here we studied two issues. One is the general performance of the proposed estimation procedure and the other is its performance when the model is misspecified. For the general performance, the left panel of part I of Table 1 shows that the proposed estimation procedure seems to work well. In particular, the proposed estimators seem unbiased, the variance estimation appears reasonable, and the normal approximation to the distribution of the estimated regression parameters seems appropriate. More details can be found in the Supplementary Material.

On model misspecification, we considered three aspects. The first is misspecifying the association parameter τ, with simulation results given in the right panel of parts I and II of Table 1. The second is misspecifying the copula function C, with simulation results given in the left panel of parts III and IV of Table 1. The last is misspecifying both τ and C; see the right panel of parts III and IV of Table 1. When the degree of association τ is misspecified, the estimators for regression parameters β can be biased. In particular, the bias increases when the assumed τ moves away from the truth and also may depend on the specified copula function. When the copula model is misspecified but the degree of association is correctly specified, the estimators for regression parameters β could be biased too if τ is far from zero. When the association is weak, all copulas are similar and thus it is expected that the estimators would be insensitive to the misspecification of copula functions. In contrast, the estimators for the regression parameters γ seem to be insensitive to the misspecification of either the copula model or the association parameter. We also considered some other set-ups, with similar conclusions.

Table 2. *Estimated dose effects under model* (4)

	$\hat{\beta}$			$\hat{\gamma}$		
τ	Estimate	SEE $\times 10^2$		Estimate	SEE $\times 10^2$	AIC
			$k_n = 3$			
−2/9	2·00	5		1·36	20	1083·13
−1/9	2·13	35		1·40	20	1080·08
0	2·28	40		1·41	20	1077·82
1/9	2·42	37		1·42	20	1076·56
2/10	2·46	36		1·42	20	1076·21
2/9	2·47	36		1·41	20	1076·22
			$k_n = 5$			
−2/9	2·03	36		1·32	20	1063·92
−1/9	2·10	35		1·36	20	1059·39
0	2·28	40		1·38	20	1057·00
1/9	2·41	37		1·38	20	1055·97
2/10	2·46	36		1·38	20	1055·45
2/9	2·46	36		1·38	20	1055·35

SEE, estimated standard error.

5. AN APPLICATION

In this section, we apply the proposed methodology to a set of current status data arising from a 2-year tumorigenicity study conducted by National Toxicology Program, analysed by Wang et al. (2008), among others. In the study, the groups of 50 male and 50 female F344/N rats and B6C3F$_1$ mice were exposed to chloroprene at concentrations of 0, 12·8, 32, or 80 ppm by inhalation, 6 h per day, 5 days per week, for 2 years. Each animal was examined for various tumors at its death. Some animals died naturally during the study and those alive at the end of study were sacrificed. Since the tumor status was examined only at death, only current status data are available for the tumor onset time, the variable of interest. One objective of the study is to compare the tumor growth rates between the different dose groups and investigate the dose effect. Following Wang et al. (2008), we will focus on a specific type of lung tumor, the alveolar/bronchiolar adenoma, for the B6C3F$_1$ mice in the control group with no chloroprene inhalation and the high dose group with 80 ppm chloroprene inhalation. Each group has 100 B6C3F$_1$ mice.

For the analysis, define T_i to be the tumor onset time and C_i the death time in months up to 25 months, the end of the study, associated with the ith animal. Also define $Z_i = 1$ if the ith mouse is in the high dose group and $Z_i = 0$ if the ith mouse is in the control group. For both groups, many mice survived to the end of the study, so, we have right-censored data on the death times C_i. To apply the proposed estimation procedure, we employed quadratic splines and considered the three copula models investigated in the simulation study with $k_n = 3$, 4, 5, or 6 and different values of τ. For each set-up, we calculated the AIC and found that the smallest AIC is given by model (4) with $k_n = 5$ and $\tau = 2/9$. Many AIC values are quite close.

Table 2 presents the estimated dose effects, obtained with the use of model (4), $k_n = 5$ and several values of τ along with the estimated standard errors. For comparison, the results obtained with $k_n = 3$ are also included. All results gave p-values smaller than 0·001 for testing no-dose effect, suggesting a strong dose effect. High-dose chloroprene significantly increased the tumor onset rate. The results obtained under other copula models gave similar conclusions and are also similar to those given in Wang et al. (2008).

6. CONCLUDING REMARKS

We have assumed that the copula model and the association parameter are known, as it is usually difficult or impossible to estimate them without strong assumptions, for example, that both marginal distributions are known, and the copulas also have to satisfy some additional conditions (Schwarz et al. , 2013), which have limited practical relevance. We assume that both the failure time of interest and the observation time

follow the proportional hazards models. Sometimes one may need or want to consider different models. It is straightforward to generalize the proposed method to other models such as the additive hazards model and the linear transformation model (Zhang et al., 2005).

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Supplementary material

Supplementary material available at *Biometrika* online includes additional simulation results and the proofs of the three theorems.

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