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STATISTICAL ANALYSIS OF THE GENERALIZED ADDITIVE SEMIPARAMETRIC SURVIVAL MODEL WITH RANDOM COVARIATES

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Generalizations of the additive hazards model are considered. Estimates of the regression parameters and baseline function are proposed, when covariates are random. The asymptotic properties of estimators are considered.

Keywords: Generalized additive model, semiparametric models, survival analysis, regression parameters, baseline function, asymptotical analysis, additive hazards.

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1. INTRODUCTION

Models describing the dependence of lifetimes distributions on explanatory variables have been considered. A number of such models was proposed by Andersen, Borgan, Gill and Keiding (1993), Cox and Oakes (1984), Dabrowska and Doksum (1988), Droesbeke, Fichet and Tassi (1989), Kalbfleisch and Prentice (1980), Lin and Ying (1994),(1996), etc. Bagdonavičius and Nikulin (1994)-(1996) proposed a general approach, which gives the possibility of formulating a number of new models and showing where known models fit into the proposed new classes.

Suppose that a time to failure $T_{x(\cdot)}$ is a nonnegative random variable with the survival function $S_{x(\cdot)}(t) = P\{T_{x(\cdot)} > t\}$ which depends on a vector of *stresses*

$$x : [0, +\infty) \to B \subset \mathbb{R}^m.$$

The time to failure $T_{x(\cdot)}$ could be called the resource of this item. But the notion of the resource should not depend on $x(\cdot)$. So we will call *the uniform resource* to the random variable $R^U = 1 - S_{x(\cdot)}(T_{x(\cdot)})$. It takes values in the interval $[0,1)$ and does not depend on $x(\cdot)$. Note that $T_{x(\cdot)} = t$ if and only if $R^U = 1 - S_{x(\cdot)}(t)$. So the number $1 - S_{x(\cdot)}(t) \in [0,1)$ is called *the uniform resource used until the moment t under the stress* $x(\cdot)$. The concrete item which failed at the moment t under the stress $x(\cdot)$ used $1 - S_{x(\cdot)}(t)$ of the resource. Instead of the uniform resource one can define a resource with any probability distribution, so we can consider a whole class of resources. Really, suppose that G is some fixed survival function, strictly decreasing and continuous on the support $[a,b]$, $-\infty \le a < b \le \infty$, $G(a) = 1$, $G(b) = 0$. $H = G^{-1}$. The functional

$$f^G_{x(\cdot)}(t) = \left(H \circ S_{x(\cdot)}\right)(t),$$

is called the *G-transfer functional*. The survival function of the random variable $R^G = f^G_{x(\cdot)}(T_{x(\cdot)})$ is G and does not depend on $x(\cdot)$. The random variable R^G is called the *G-resource* and the number $f^G_{x(\cdot)}(t)$ is called the *G-resource used till the moment* t. Denote by $\mathcal{G}$ the family of survival functions, continuous and decreasing on their supports. Consider the class of transfer functionals $\mathcal{M} = \{f^G, \quad G \in \mathcal{G}\}$. Models will be formulated in dependence on properties of the transfer functionals. Note that some assumptions may be satisfied by one transfer functional, but not satisfied by another. This is the cause of considering the *whole class of resources*.

In the case of $G(t) = e^{-t}1_{[0,\infty[}(t)$ the transfer functional has the form $f^G_{x(\cdot)}(t) = -\ln S_{x(\cdot)}(t)$ and the rate of resource use is

$$\frac{\partial f^G_{x(\cdot)}(t)}{\partial t} = \alpha_{x(\cdot)}(t),$$

where $\alpha_{x(\cdot)}(t) = -S'_{x(\cdot)}(t)/S_{x(\cdot)}(t)$ is the hazard rate of $T_{x(\cdot)}$.

The additive hazards model (AHM) (see Andersen et al. (1993)) holds on E if there exist functions λ_0 and a such that for all $x(\cdot) \in E$

$$\alpha_{x(\cdot)}(t) = \alpha_0(t) + a[x(t)].$$

Now we generalize this model.

Definition. *The G-generalized additive model holds on E if there exists a function $a(\cdot)$ on E and a survival function S_0 such that, for all $x(\cdot) \in E$, the transfer functional $f^G \in \mathcal{M}$ satisfies the differential equation*

$$\frac{\partial f^G_{x(\cdot)}(t)}{\partial t} = \frac{\partial f^G_0(t)}{\partial t} + a(x(t)) \tag{1}$$

with the initial conditions $f^G_0(0) = f^G_{x(\cdot)}(0) = 0$.

So the stress influences additively the rate of resource use. Equation (1) implies that

$$S_{x(\cdot)}(t) = G\{f^G_0(t) + \int_0^t a[x(\tau)]d\tau\}.$$

Let us consider some particular models different from AHM.

1. Taking $G(t) = \exp\{-\exp\{t\}\}$, for $t \in R^1$, we obtain

$$\frac{\partial f^G_{x(\cdot)}(t)}{\partial t} = \frac{\alpha_{x(\cdot)}(t)}{A_{x(\cdot)}(t)}, \quad \frac{\partial f^G_0(t)}{\partial t} = \frac{\alpha_0(t)}{A_0(t)},$$

where

$$A_{x(\cdot)}(t) = \int_0^t \alpha_{x(\cdot)}(\tau)d\tau, \quad A_0(t) = \int_0^t \alpha_0(\tau)d\tau$$

are the cumulated hazards rates. So we have the model:

$$\frac{\alpha_{x(\cdot)}(t)}{A_{x(\cdot)}(t)} = \frac{\alpha_0(t)}{A_0(t)} + a(x(t)).$$

2. Taking $G(t) = 1/(1+t)$, for $t \geq 0$, we obtain

$$\frac{\alpha_{x(\cdot)}(t)}{S_{x(\cdot)}(t)} = \frac{\alpha_0(t)}{S_0(t)} + a(x(t)).$$

3. Taking $G(t) = 1/(1+e^t)$, for $t \in R^1$, we obtain

$$\frac{\alpha_{x(\cdot)}(t)}{1-S_{x(\cdot)}(t)} = \frac{\alpha_0(t)}{1-S_0(t)} + a(x(t)).$$

4. Take $G(t) = 1 - \Phi(\ln t)$, $t \geq 0$, where $\Phi(\cdot)$ is the normal $N(0,1)$ cumulative distribution function. In terms of survival functions we obtain the model :

$$\Phi^{-1}(1 - S_{X(\cdot)}(t)) = \ln\left\{\int_0^t a[x(\tau)]d\tau + \exp[\Phi^{-1}(1 - S_0(t))]\right\}.$$

5. Taking $G = S_0$, we obtain

$$S_{X(\cdot)}(t) = S_0\{\int_0^t \sigma[x(\tau)]d\tau\},$$

where $\sigma[x(t)] = 1 + a[x(t)]$. It is the *accelerated life model*.

Other distributions of the resource can be taken.

So a number of alternatives to the AHM is proposed. For example, if at the beginning of life data follow well the AHM but later it is not so, the model of example **2** could be choosed. On the contrary, if at the beginning of life data do not follow the AHM but at the end of life this model suits well, the model of example **3** could be choosed.

2. ESTIMATION

2.1. Notations

Consider the model (1) with some specified G and an unknown baseline survival function S_0.

The function $a[x(\cdot)]$ is parametrized as follows:

$$a[x(t)] = \gamma^T x(t),$$

where $\gamma = (\gamma_1, \ldots, \gamma_m)^T$ is the vector of unknown regression parameters. So the following model is considered: for all $x(\cdot) \in E$

$$S_{X(\cdot)}(t) = G\{H(S_0(t)) + \int_0^t \gamma^T x(\tau)d\tau\}. \tag{2}$$

Suppose that n individuals are observed and assume that the vector of covariates for the ith individual is a random process $X_i(\cdot) = (X_{i1}(\cdot), \ldots, X_{im}(\cdot))^T$.

Denote by $N_i(t)$ the univariate counting processes. This process counts the numbers of observed failures of each individual in the interval $[0,t]$, $t \geq 0$. Denote by

$Y_i(t)$ the numbers of individual " at risk" (non-censored and non-failed) just prior to t for each i.

Suppose that $\{\mathcal{F}_t, t \geq 0\}$ is the filtration generated by

$$\{N_i(s), Y_i(s), X_i(s), i = 1, \ldots, n; 0 \leq s \leq t\},$$

X_i are predictable and the intensities λ_i, given by

$$\lambda_i(t) = \lim_{\varepsilon \downarrow 0} \frac{1}{\varepsilon} P\{N_i(t+\varepsilon) - N_i(t) \geq 1 | \mathcal{F}_{t-}\},$$

exist. In this case the compensators of the counting processes $N_i(t)$ are

$$\Lambda_i(t) = \int_0^t \lambda_i(s) ds.$$

Assume that the random intensities λ_i satisfy the *multiplicative intensity model*

(3)
$$\lambda_i(t) = \alpha_{X_{i(\cdot)}}(t) Y_i(t).$$

Denote

$$N(t) = \sum_{i=1}^n N_i(t), \quad Y(t) = \sum_{i=1}^n Y_i(t), \quad \Lambda(t) = \sum_{i=1}^n \Lambda_i(t), \quad M_i(t) = N_i(t) - \Lambda_i(t),$$

$$M(t) = \sum_{i=1}^n M_i(t), \quad J(s) = I(Y(s) > 0), \quad \alpha = -\frac{G'}{G}, \quad \psi = \alpha \circ H.$$

The hazard rates $\alpha_{X_{i(\cdot)}}(t)$ have the form

(4)
$$\alpha_i(t) = \alpha_{X_{i(\cdot)}}(t) = \psi(S_{X_{i(\cdot)}}(t))\{(H \circ S_0)'(t) + \gamma^T X_i(t)\}.$$

2.2. Estimating equation and estimators $\tilde{H}_0$, $\hat{\gamma}$ and $\hat{S}_{X(\cdot)}$

From the Doob-Meyer decomposition $N = M + \Lambda$, equalities (3) and (4) imply

$$dN(t) = dM(t) + \sum_{i=1}^n \psi(S_{X_{i(\cdot)}}(t)) Y_i(t)\{dH(S_0(t)) + \gamma^T X_i(t) dt\}$$

and

$$\int_0^t \frac{J(u)(dN(u) - S_*^{(0)}(\gamma, u) du)}{S^{(0)}(\gamma, u)} = \int_0^t J(u) dH(S_0(u)) + \int_0^t \frac{J(u) dM(u)}{S^{(0)}(\gamma, u)},$$

where

$$S^{(0)}(\gamma,u)=\sum_{i=1}^{n}Y_i(u)\psi(S_{X_{i(\cdot)}}(u)),$$

$$S_*^{(0)}(\gamma,u)=\sum_{i=1}^{n}Y_i(u)\psi(S_{X_{i(\cdot)}}(u))\gamma^T X_i(u).$$

Under some mild assumptions M is a martingale, therefore

$$E\int_0^t \frac{J(u)(dN(u)-S_*^{(0)}(\gamma,u)du)}{S^{(0)}(\gamma,u)}=E\int_0^t J(u)dH(S_0(u)). \tag{5}$$

If $Y(t)>0$, then

$$\int_0^t J(u)dH(S_0(u))=H(S_0(t)). \tag{6}$$

Equalities (5) and (6) imply that a reasonable estimator $\hat{H}_0(t,\gamma)$ for $H_0(t)=H(S_0(t))$ (still depending on γ) is determined by the equation

$$\hat{H}_0(t,\gamma)=\int_0^t J(u)\frac{dN(u)-\tilde{S}_*^{(0)}(\gamma,u)du}{\tilde{S}^{(0)}(\gamma,u)},$$

where

$$\tilde{S}^{(0)}(\gamma,u)=\sum_{i=1}^{n}Y_i(u)\alpha(\hat{H}_i(u,\gamma)),\quad \tilde{S}_*^{(0)}(\gamma,u)=\sum_{i=1}^{n}Y_i(u)\alpha(\hat{H}_i(u,\gamma))\gamma^T X_i(u),$$

$$H_i(u,\gamma)=H_0(u)+\int_0^u \gamma^T X_i(\tau)d\tau,\quad \hat{H}_i(u,\gamma)=\hat{H}_0(u-,\gamma)+\int_0^u \gamma^T X_i(\tau)d\tau.$$

Denote $\tau^*=\sup\{t:Y(t)>0\}$. Suppose that at the non-random moment $\tau\in]0,\infty]$ all the individuals are censored, i.e., $\tau^*\le\tau$. We propose to estimate the parameter γ by solving the estimating equations

$$U(\gamma,\tau)=0,$$

where the estimating function is given by the formula below

$$U(\gamma,t)=\sum_{i=1}^{n}\int_0^t J(u)X_i(u)\{dN_i(u)-Y_i(u)\alpha(\hat{H}_i(u,\gamma))d\hat{H}_i(u,\gamma)\}.$$

Those equations generalize the estimating equations of Lin and Ying (1994) for the additive hazards model (taking $\alpha(p)\equiv 1$).

If we denote by $\hat{\gamma}$ the estimator of γ, i.e. $U(\hat{\gamma},\tau)=0$, then the estimator of the function $H_0(t)$ is

$$\tilde{H}_0(t)=\hat{H}_0(t,\hat{\gamma}) \tag{7}$$

and the estimator of the survival function $S_{x(\cdot)}(t)$ under any covariate $x(\cdot)$ is

$$\hat{S}_{x(\cdot)}(t)=G\left\{\tilde{H}_0(t)+\int_0^t \hat{\gamma}^T x(u)du\right\}. \tag{8}$$

Let

$$\tilde{S}^{(1)}(\gamma,u)=\sum_{i=1}^n X_i(u)Y_i(u)\alpha(\hat{H}_i(u,\gamma)),$$

$$\tilde{S}_*^{(1)}(\gamma,u)=\sum_{i=1}^n X_i(u)Y_i(u)\alpha(\hat{H}_i(u,\gamma))\gamma^T X_i(u),$$

$$\tilde{E}(\gamma,u)=\frac{\tilde{S}^{(1)}(\gamma,u)}{\tilde{S}^{(0)}(\gamma,u)}.$$

Then the estimating function $U(\gamma,t)$ can be written

$$U(\gamma,t)=\sum_{i=1}^n\int_0^t J(u)\{X_i(u)-\tilde{E}(\gamma,u)\}\left\{dN_i(u)-Y_i(u)\alpha(\hat{H}_i(u,\gamma))\gamma^T X_i(u)du\right\}. \tag{9}$$

3. ASYMPTOTIC PROPERTIES OF THE ESTIMATORS

3.1. Asymptotic properties of the estimating function

Denote by $||A||=\sup_{i,j}|a_{ij}|$ the norm of any matrix A, by γ_0 the true value of the parameter γ,

$$S^{(1)}(\gamma,u)=\sum_{i=1}^n X_i(u)Y_i(u)\alpha(H_i(u,\gamma)),$$

$$S_*^{(1)}(\gamma,u)=\sum_{i=1}^n X_i(u)Y_i(u)\alpha(H_i(u,\gamma))\gamma^T X_i(u),$$

$$E(\gamma,u)=\frac{S^{(1)}(\gamma,u)}{S^{(0)}(\gamma,u)},$$

$$S^{(2)}(\gamma,u)=\sum_{i=1}^n X_i(u)X_i^T(u)Y_i(u)\alpha(H_i(u)),$$

$$\tilde{S}^{(2)}(\gamma,u) = \sum_{i=1}^{n} X_i(u)X_i^T(u)Y_i(u)\alpha(\hat{H}_i(u,\gamma)),$$

$$S^{(3)}(\gamma,u) = \sum_{i=1}^{n} Y_i(u)\alpha'(H_i(u,\gamma)),$$

$$S_*^{(3)}(\gamma,u) = \sum_{i=1}^{n} Y_i(u)\alpha'(H_i(u,\gamma))\gamma^T X_i(u).$$

Assumptions A

1. Negligibility conditions.

   There exist a neighborhood Γ of γ_0 and a scalar, vector or matrix functions $s^{(0)}$, $s_*^{(0)}$, $s^{(1)}$, $s_*^{(1)}$, $s^{(2)}$, $s_*^{(2)}$, $s^{(3)}$, $s_*^{(3)}$, such that for $m = 0,1,2$:

   (a)
   $$\sup_{\gamma\in\Gamma,\, t\in[0,\tau]} \|\frac{1}{n}S^{(m)}(\gamma,t) - s^{(m)}(\gamma,t)\| \xrightarrow{P} 0,$$
   $$\sup_{\gamma\in\Gamma,\, t\in[0,\tau]} \|\frac{1}{n}S_*^{(m)}(\gamma,t) - s_*^{(m)}(\gamma,t)\| \xrightarrow{P} 0,$$

   (b) $s^{(0)}(\gamma_0,\cdot)$ is bounded away from zero on $[0,\tau]$,

   (c) $s^{(m)}(\cdot,\cdot)$, $s_*^{(m)}(\cdot,\cdot)$ are continuous functions of $\gamma \in \Gamma$ uniformly in $t \in [0,\tau]$ and bounded on $\Gamma \times [0,\tau]$.

2. $$H_0(\tau) = H(S_0(\tau)) < \infty,$$

3. α is a positive continuously differentiable on $]0,\infty[$ function,

4. $$P\{\sup_{t\in[0,\tau]} |X_{ij}(t)| < \infty\} = 1 \quad \text{for all } i,j.$$

5. $$\sigma^2(t) = \int_0^t \frac{s^{(0)}(\gamma,u)dH_0(u) + s_*^{(0)}(\gamma,u)du}{s^{(0)2}(\gamma,u)} < +\infty.$$

Lemma. *Suppose that assumptions A hold. Then*

$$\sqrt{n}\left[\hat{H}_0(t,\gamma) - H_0(t)\right] \xrightarrow{D} h(\gamma,t)\int_0^t \frac{dV(u)}{h(\gamma,u)} \quad \textit{as} \quad n\to\infty,$$

where V is the Gaussian martingale with

$$EV(t) = 0 \quad and \quad Cov(V(t), V(s)) = \sigma^2(t \wedge s),$$

$$h(\gamma, t) = \exp\left\{ -\int_0^t \frac{1}{s^{(0)}(\gamma, u)} \left(s^{(3)}(\gamma, u) dH_0(u) + s_*^{(3)}(\gamma, u) du \right) \right\}.$$

Proof: Consider the difference:

$$\sqrt{n}\left[\hat{H}_0(t,\gamma) - H_0(t)\right] = \sqrt{n}\left\{ \int_0^t J(u) \frac{dN(u) - \tilde{S}_*^{(0)}(\gamma,u)du}{\tilde{S}^{(0)}(\gamma,u)} - H_0(t) \right\} =$$

$$= \sqrt{n}\left\{ \int_0^t J(u) \left[\frac{dM(u)}{\tilde{S}^{(0)}(\gamma,u)} + \frac{S^{(0)}(\gamma,u) - \tilde{S}^{(0)}(\gamma,u)}{\tilde{S}^{(0)}(\gamma,u)} dH_0(u) + \frac{S_*^{(0)}(\gamma,u) - \tilde{S}_*^{(0)}(\gamma,u)}{\tilde{S}^{(0)}(\gamma,u)} du \right] \right\}.$$

Note that

$$\frac{1}{\sqrt{n}}\left[\tilde{S}^{(0)}(\gamma,u) - S^{(0)}(\gamma,u)\right] =$$

$$\frac{1}{n}\sum_{i=1}^{n} Y_i(u)\alpha'\{H_i(u,\gamma)\}\sqrt{n}\left[\hat{H}_0(u-,\gamma) - H_0(u)\right] + o_p(1) =$$

$$s^{(3)}(\gamma,u)\sqrt{n}[\hat{H}_0(u-,\gamma) - H_0(u)] + o_p(1).$$

Similarly

$$\frac{1}{\sqrt{n}}\left[\tilde{S}_*^{(0)}(\gamma,u) - S_*^{(0)}(\gamma,u)\right] =$$

$$s_*^{(3)}(\gamma,u)\sqrt{n}\left[\hat{H}_0(u-,\gamma) - H_0(u)\right] + o_p(1)$$

and

$$\frac{n}{\tilde{S}^{(0)}(\gamma,u)} = \frac{1}{s^{(0)}(\gamma,u)} + o_p(1).$$

So

$$\sqrt{n}\left[\hat{H}_0(t,\gamma) - H_0(t)\right] = \sqrt{n}\int_0^t \frac{J(u)dM(u)}{\tilde{S}^{(0)}(\gamma,u)} -$$

$$\int_0^t \sqrt{n}\left[\hat{H}_0(u-,\gamma) - H_0(u)\right] \frac{s^{(3)}(\gamma,u)dH_0(u) + s_*^{(3)}(\gamma,u)du}{s^{(0)}(\gamma,u)} + o_p(1).$$

Note that the predictable variation

$$< \sqrt{n}\int_0^t \frac{J(u)dM(u)}{\tilde{S}^{(0)}(\gamma,u)} >= n\int_0^t J(u)\frac{S^{(0)}(\gamma,u)dH_0(u) + S_*^{(0)}(\gamma,u)du}{\tilde{S}^{(0)2}(\gamma,u)} \xrightarrow{P} \sigma^2(t)$$

and

$$\int_0^t J(u)\frac{n}{\tilde{S}^{(0)2}(\gamma,u)} I\left\{\left|\frac{J(u)\sqrt{n}}{\tilde{S}^{(0)}(\gamma,u)}\right| > \varepsilon\right\}\left(S^{(0)}(\gamma,u)dH_0(u) + S_*^{(0)}(\gamma,u)du\right) \xrightarrow{P} 0.$$

By Rebolledo's theorem (see Andersen et al (1993)) we obtain the convergence :

$$\sqrt{n}\int_0^t \frac{J(u)dM(u)}{\tilde{S}^{(0)}(\gamma,u)} \xrightarrow{D} V(t) \quad \text{as} \quad n\to\infty.$$

Then

$$\sqrt{n}\left[\hat{H}_0(t,\gamma) - H_0(t)\right] \xrightarrow{D} h(\gamma,t)\int_0^t \frac{dV(u)}{h(\gamma,u)} \quad \text{as} \quad n\to\infty.$$

The proof is completed.

■

Corollary. *Under assumptions A*

$$\sqrt{n}\left[\hat{H}_0(t,\gamma) - H_0(t)\right] = h(\gamma,t)\sqrt{n}\int_0^t \frac{J(u)dM(u)}{h(\gamma,u)S^{(0)}(\gamma,u)} + o_P(1). \tag{10}$$

Consider the asymptotical distribution of the score function $U(\gamma_0,\tau)$. The Doob-Meyer decomposition and equality (9) imply

$$\frac{1}{\sqrt{n}}U(\gamma_0,t) = \frac{1}{\sqrt{n}}U^*(\gamma_0,t) + \frac{1}{\sqrt{n}}\Delta(\gamma_0,t) + o_P(1),$$

where

$$\frac{1}{\sqrt{n}}U^*(\gamma_0,t)) = \frac{1}{\sqrt{n}}\sum_{i=1}^n\int_0^t J(u)\{X_i(u) - E(\gamma_0,u) + \frac{1}{h(\gamma_0,u)S^{(0)}(\gamma_0,u)}\times$$

$$\sum_{j=1}^n\left[\int_u^t J(s)[X_i(s) - E(\gamma_0,s)]\alpha'(H_j(s,\gamma))h(\gamma_0,s)Y_j(s)\times\right.$$

$$\left.\left(dH_0(s) + \gamma_0^T X_j(s)ds\right)\right]\}dM_i(u) \tag{11}$$

and

$$\frac{1}{\sqrt{n}}\Delta(\gamma_0,t) = -\int_0^t J(s)[\tilde{E}(\gamma_0,s) - E(\gamma_0,s)]dM(s)+$$

$$\int_0^t J(s)[\tilde{E}(\gamma_0,s)-E(\gamma_0,s)][\tilde{S}^{(0)}(\gamma_0,s)-S^{(0)}(\gamma_0,s)]dH_0(s)+$$
$$\int_0^t J(s)[\tilde{E}(\gamma_0,s)-E(\gamma_0,s)]\left\{\alpha(\hat{H}_i(s,\gamma_0))-\alpha(H_i(s))\right\}\gamma_0^T X_i(s)Y_i(s)ds.$$

Thus the problem is to prove that $\frac{1}{\sqrt{n}}U^*(\gamma_0,t))$ converges to a Gaussian martingale and $\frac{1}{\sqrt{n}}\Delta(\gamma_0,t)$ converges to 0 in probability.

The integral (11) is a local martingale as an integral of a locally bounded predictable process with respect to a martingale, so the central limit theorem for martingales (Rebolledo's theorem, see Andersen et al. (1993), p.83) can be applied. The limit process of $\frac{1}{\sqrt{n}}U^*(\gamma_0,t))$ would be a Gaussian martingale if the predictable covariation process $< n^{-1/2}U^* > (\gamma_0,t)$ would converge to some non-random matrix and the generalized Lindenberg condition would be satisfied. Note that the predictable covariation process

$$< n^{-1/2}U^* > (\gamma_0,t) = \frac{1}{n}\sum_i \int_0^t J(u)\left\{X_i(u)-E(\gamma_0,u)+\frac{1}{h(\gamma_0,u)S^{(0)}(\gamma_0,u)}\times\right.$$
$$\left.\sum_j\left[\int_u^t [X_j(s)-E(\gamma_0,s)]\alpha'(H_j(s,\gamma))h(\gamma_0,s)Y_j(s)\left(dH_0(s)+\gamma_0^T X_j(s)ds\right)\right]\right\}^{\otimes 2}\times$$
$$Y_i(u)\alpha(H_i(u,\gamma))\left[dH_0(u)+\gamma_0^T X_i(u)du\right]. \tag{12}$$

Hence to obtain the limit distribution of $\frac{1}{\sqrt{n}}U^*(\gamma_0,t))$ the assumption that the process (12) converges in probability to some non-degenerate non-random matrix must be made. Note that this process has the form $\frac{1}{n}\sum_{i=1}^n \xi_i(t)$ and if the covariates $X_i(\cdot)$ are not behaving in some strange way (increasing very quickly and so on), this convergence is natural.

Therefore we formulate

Stability condition:
$$< n^{-1/2}U^* > (\gamma_0,t) \xrightarrow{P} \Sigma(\gamma_0,t),$$
where $\Sigma(\gamma_0,t)$ is non-random and non-degenerated matrix.

Theorem 1. *Suppose that assumptions A and the stability condition hold. Then, as* $n\to\infty$
$$n^{-1/2}U(\gamma_0,\tau) \xrightarrow{D} N(0,\Sigma(\gamma_0,\tau)).$$

Proof: It is sufficient to prove that the Lindenberg condition is satisfied. Denote

$$H_{il}(u) = J(u)\{X_{il}(u) - E_l(\gamma_0, t) + \frac{1}{h(\gamma_0, u)S^{(0)}(\gamma_0, u)}$$

$$\sum_{j=1}^{n} \int_u^t [X_{il}(s) - E_l(\gamma_0, s)]\alpha'(H_j(s,\gamma))h(\gamma_0, s)Y_j(s)\left(dH(S_0(s)) + \gamma_0^T X_j(s)ds\right)\},$$

where $E_l(\gamma_0, s))$ is a lth component of the vector $E(\gamma_0, s)$. The Lindenberg condition in our case is

$$\frac{1}{n}\sum_i \int_0^t H_{il}^2(u)I\{\frac{1}{\sqrt{n}} \mid H_{il}(u) \mid > \varepsilon\}Y_i(u)\alpha_i(s)ds \xrightarrow{P} 0.$$

But it is obvious as by assumptions of the theorem $H_{ij}(u)$ are bounded on $[0,\tau]$ and

$$\int_0^\tau \alpha_i(s)ds < \infty.$$

By Rebolledo's theorem

$$n^{-1/2}U^*(\gamma_0, \tau) \xrightarrow{D} N(0, \Sigma(\gamma_0, \tau)).$$

The term $n^{-1/2}\Delta$ converges in probability to zero. It can be seen similarly as in Bagdonavičius & Nikulin (1996) by applying Lenglart's inequality.

The proof of the theorem 1 is completed.

■

3.2. Asymptotic properties of the estimator $\hat{\gamma}$.

Let

$$e(\gamma, u) = \frac{s^{(1)}(\gamma, u)}{s^{(0)}(\gamma, u)},$$

$$S_*^{(4)}(\gamma, u) = \sum_{i=1}^{n}\{X_i(u) - E(\gamma, u)\}Y_i(u)\alpha'(H_i(u,\gamma))\int_0^u X_i^T(\tau)d\tau\gamma^T X_i(u).$$

Assumptions B

1. Negligibility condition:

$$\sup_{\gamma\in\Gamma, t\in[0,T]} \left\| \frac{1}{n}S_*^{(4)}(\gamma, u) - s_*^{(4)}(\gamma, u)\right\| \xrightarrow{P} 0.$$

2. The matrix

$$\Sigma_1(\gamma_0,\tau) = \int_0^\tau \left\{ \frac{\partial}{\partial\gamma} e(\gamma_0,u) s^{(0)}(\gamma_0,u) dH_0(u) + \left[s_*^{(4)}(\gamma_0,u) + s^{(2)}(\gamma_0,u) - e(\gamma_0,u) s^{(1)T}(\gamma_0,u) \right] du \right\}$$

is non degenerated.

Theorem 2. *Suppose assumptions B and those of the Theorem 1 hold. Then there exists a neighborhood of γ_0 within which, with probability tending to 1 as $n \to \infty$, the root $\hat{\gamma}$ of $U(\gamma,\tau) = 0$ is uniquely defined and*

$$n^{1/2}(\hat{\gamma} - \gamma_0) \xrightarrow{D} N(0, \Sigma_2(\gamma_0,\tau)), \tag{13}$$

where

$$\Sigma_2(\gamma_0,t) = \Sigma_1^{-1}(\gamma_0,t) \Sigma(\gamma_0,t) \Sigma_1^{-1}(\gamma_0,t).$$

Proof: Using the Taylor expansion of $n^{-1/2}U(\gamma,\tau)$ around γ_0 in $\gamma = \hat{\gamma}$, we obtain

$$n^{1/2}(\hat{\gamma} - \gamma_0) = \left(-\frac{1}{n} \frac{\partial U(\gamma^*,\tau)}{\partial\gamma} \right)^{-1} n^{-1/2} U(\gamma_0,\tau), \tag{14}$$

where γ^* is on the line segment between $\hat{\gamma}$ and γ_0. Theorem 1 implies, that the convergence (13) is proved if we prove that

$$-\frac{1}{n} \frac{\partial U(\gamma_0,\tau)}{\partial\gamma} \xrightarrow{P} \Sigma_1(\gamma_0,\tau) \quad \text{and} \quad \hat{\gamma} \xrightarrow{P} \gamma_0.$$

We have

$$-\frac{1}{n} \frac{\partial U(\gamma,\tau)}{\partial\gamma} = \frac{1}{n} \sum_{i=1}^n \int_0^\tau J(u) \frac{\partial}{\partial\gamma} \tilde{E}(\gamma,u) \{ dM_i(u) + Y_i(u) \alpha(H_i(u,\gamma)) dH_0(u) + Y_i(u) \gamma^T X_i(u) \left[\alpha(H_i(u,\gamma)) - \alpha(\hat{H}_i(u,\gamma)) \right] du \} + \frac{1}{n} \sum_{i=1}^n \int_0^\tau J(u) \{ X_i(u) - \tilde{E}(\gamma,u) \} \times Y_i(u) \left[\frac{\partial}{\partial\gamma} \alpha(\hat{H}_i(u,\gamma)) \gamma^T X_i(u) + \alpha(\hat{H}_i(u,\gamma)) X_i^T(u) \right] du.$$

Note that

$$\frac{1}{n} \sum_{i=1}^n \int_0^\tau J(u) \frac{\partial}{\partial\gamma} \tilde{E}(\gamma,u) dM_i(u) \xrightarrow{P} 0,$$

$$\frac{1}{n}\sum_{i=1}^{n}\int_0^\tau J(u)\frac{\partial}{\partial\gamma}\tilde{E}(\gamma,u)Y_i(u)\alpha(H_i(u,\gamma))dH_0(u)\xrightarrow{P}\int_0^\tau\frac{\partial}{\partial\gamma}e(\gamma,u)s^{(0)}(u,\gamma)dH_0(u),$$

$$\frac{1}{n}\sum_{i=1}^{n}\int_0^\tau J(u)\frac{\partial}{\partial\gamma}\tilde{E}(\gamma,u)Y_i(u)\gamma^T X_i(u)\left[\alpha(\hat{H}_i(u,\gamma))-\alpha(H_i(u,\gamma))\right]du\xrightarrow{P}0,$$

$$\frac{1}{n}\sum_{i=1}^{n}\int_0^\tau J(u)\{X_i(u)-\tilde{E}(\gamma,u)\}Y_i(u)\frac{\partial}{\partial\gamma}\alpha(\hat{H}_i(u,\gamma))\gamma^T X_i(u)du\xrightarrow{P}\int_0^\tau s_*^{(4)}(\gamma,u)du,$$

$$\frac{1}{n}\sum_{i=1}^{n}\int_0^\tau J(u)\{X_i(u)-\tilde{E}(\gamma,u)\}Y_i(u)\alpha[\hat{H}_i(u,\gamma)]\gamma^T X_i(u)du\xrightarrow{P}$$

$$\int_0^\tau\left[s^{(2)}(\gamma,u)-e(\gamma,u)s^{(1)}(\gamma,u)\right]du.$$

Therefore

$$-\frac{1}{n}\frac{U(\gamma_0,\tau)}{\partial\gamma}\xrightarrow{P}\Sigma_1(\gamma_0,\tau). \tag{15}$$

In the rest of the proof we follow Lin and Ying (1996). By assumptions of the theorem, for any $\varepsilon>0$, we can choose $\delta>0$ such that for all n

$$\|\frac{1}{n}\frac{\partial}{\partial\gamma}U(\gamma,\tau)-\frac{1}{n}\frac{\partial}{\partial\gamma}U(\gamma_0,\tau)\|<\varepsilon$$

whenever $\|\gamma-\gamma_0\|<\delta$. On the other hand the convergence (15) implies that

$$P\{\sup_{\|\gamma-\gamma_0\|\le\delta}\|-\frac{1}{n}\frac{\partial}{\partial\gamma}U(\gamma,\tau)-\Sigma_1(\gamma_0,\tau)\|>2\varepsilon\}\to 0 \tag{16}$$

as $n\to\infty$.

Now we apply the theorem about the inverse mapping, which states that if $f(u),u\in R^p$ is continuosly differentiable at u_0 and $\partial f(u_0)/\partial u$ is nonsingular, then there exist δ_0 and ε_0 that f is a one-to-one mapping on $B(u_0,\delta_0)$, the ball centered of the u_0 with radius δ_0 and $f(B(u_0,\delta_0))\supset B(f(u_0),\varepsilon_0)$. As noted by Lin and Ying that result holds simultaneously for a family of such functions with common δ_0 and ε_0 as long as their derivatives at u_0 are sufficiently close. This result and (16) imply that there exist δ_1 and ε_1 such that $n^{-1}U(\cdot,\tau)$ is one-to-one mapping from the $B(\gamma_0;\delta_1)$ to $n^{-1}U(B(\gamma_0,\delta_1),\tau)$, which contains $B(n^{-1}U(\gamma_0,\tau),\varepsilon_1)$. Since

$$n^{-1}U(\gamma_0,\tau)\xrightarrow{P}\int_0^\tau[s^{(1)}(u,\gamma_0)-e(u,\gamma_0)]s^{(0)}(u,\gamma_0)dH_0(u)=0,$$

we have

$$P\{0\in B(n^{-1}U(\gamma_0;t);\varepsilon_1)\}\to 1\quad\text{as}\quad n\to\infty.$$

Therefore

$$P\{\hat{\gamma} \quad \text{exists and is unique in} \quad B(\gamma_0,\delta_1)\} \to 1 \quad \text{and} \quad \hat{\gamma} \xrightarrow{P} \gamma_0.$$

Consider the equality (14). If $n \to \infty$, then

$$\gamma^* \xrightarrow{P} \gamma_0 \quad \text{and} \quad -\frac{1}{n}\frac{\partial U(\gamma^*,\tau)}{\partial \gamma} \xrightarrow{P} \Sigma_1(\gamma_0,\tau),$$

hence the convergence (13). The proof of the theorem 2 is complete.

■

3.3. Asymptotic properties of $\tilde{H}_0$ and $\hat{S}_{x(\cdot)}$

Now we will consider the asymptotic distribution of the estimator of the function H_0. Denote

$$\sigma_1^2(\gamma_0,t) = \int_0^t \frac{s^{(0)}(\gamma_0,u)dH_0(u) + s_*^{(0)}(\gamma_0,u)du}{(s^{(0)})^2(\gamma_0,u)},$$

$$H_i(\gamma_0,u) = J(u)\{X_i(u) - E(\gamma_0,u) + \frac{1}{h(\gamma_0,u)S^{(0)}(\gamma_0,u)} \times$$

$$\sum_{j=1}^n \left[\int_u^t J(s)[X_j(s) - E(\gamma_0,s)]\alpha'(H_j(s))h(\gamma_0,s)Y_j(s)\left(dH_0(s) + \gamma_0^T X_j(s)ds\right)\right]\}.$$

Assumptions C (Stability conditions)

1.
$$\sum_{i=1}^n \int_0^t \frac{H_i(\gamma_0,u)}{\tilde{S}^{(0)}(\gamma_0,u)} \alpha(H_i(\gamma_0,u))Y_i(u)\left(dH_0(u) + \gamma_0^T X_i(u)du\right) \xrightarrow{P} A(\gamma_0,t).$$

2.
$$\int_0^t J(u)\left\{\frac{\partial}{\partial\gamma}\left(\frac{1}{\tilde{S}^{(0)}(\gamma^*,u)}\right)\left[S^{(0)}(\gamma_0,u)dH_0(u) + \tilde{S}_*^{(0)}(\gamma^*,u)du\right] - \frac{\partial}{\partial\gamma}\left(\frac{\tilde{S}_*^{(0)}(\gamma^*,u)}{\tilde{S}^{(0)}(\gamma^*,u)}\right)du\right\} \xrightarrow{P} C(\gamma_0,t).$$

Theorem 3. *Under assumptions C and those of Theorem 2 for all $t \in [0,\tau]$*

$$n^{1/2}\{\tilde{H}_0(t) - H_0(t)\} \xrightarrow{D} N(0,\sigma_2^2(\gamma_0,t)) \quad \text{as} \quad n \to \infty,$$

where

$$H_0(t) = H(S_0(t)), \quad \tilde{H}_0(t) = \hat{H}_0(t, \hat{\gamma}),$$
$$\sigma_2^2(\gamma_0, t) = \sigma_1^2(\gamma_0, t) + C(\gamma_0, t))\Sigma_2(\gamma_0, \tau)C^T(\gamma_0, t) - 2C(\gamma_0, t)\Sigma_1^{-1}(\gamma_0, \tau)A(\gamma_0, t).$$

Proof: By Taylor expansion around γ_0 the random process $\sqrt{n}\{\tilde{H}_0(t) - H_0(t)\}$ can be written in the following manner:

$$\sqrt{n}\{\tilde{H}_0(t) - H_0(t)\} = n^{1/2}\left\{\int_0^t \frac{J(u)}{\tilde{S}^{(0)}(\hat{\gamma}, u)}(dN(u) - \tilde{S}_*^{(0)}(\hat{\gamma}, u)du) - H_0(t)\right\} =$$

$$n^{1/2}\left\{\int_0^t \frac{J(u)}{\tilde{S}^{(0)}(\gamma_0, u)}(dN(u) - \tilde{S}_*^{(0)}(\gamma_0, u)du) - \int_0^t J(u)\frac{\partial}{\partial\gamma}\left(\frac{1}{\tilde{S}^{(0)}(\gamma^*, u)}\right)dN(u)(\hat{\gamma} - \gamma_0) + \right.$$
$$\left.\int_0^t J(u)\frac{\partial}{\partial\gamma}\left(\frac{\tilde{S}_*^{(0)}(\gamma^*, u)}{\tilde{S}^{(0)}(\gamma^*, u)}\right)du(\hat{\gamma} - \gamma_0) - H_0(t)\right\} =$$

$$n^{1/2}\{C(\gamma_0, t)(\hat{\gamma} - \gamma_0) + \int_0^t J(u)\frac{dM(u)}{\tilde{S}^{(0)}(\gamma_0, u)}\} + o_p(1), \tag{17}$$

where γ^* is on the line segment between $\hat{\gamma}$ and γ_0. Taking into account (15), we obtain

$$n^{1/2}(\hat{\gamma} - \gamma_0) = \Sigma_1^{-1}(\gamma_0, \tau)n^{-1/2}U(\gamma_0, \tau) + o_p(1).$$

From theorem 1:

$$n^{-1/2}U(\gamma_0, \tau) = n^{-1/2}\sum_{i=1}^n \int_0^\tau H_i(\gamma_0, u)dM_i(u) + o_p(1).$$

Therefore the predictable covariation

$$< n^{-1/2}\sum_{i=1}^n \int_0^\tau H_i(\gamma_0, u)dM_i(u), n^{1/2}\int_0^t J(u)\frac{dM(u)}{\tilde{S}^{(0)}(\gamma_0, u)} >=$$

$$\sum_{i=1}^n \int_0^t \frac{H_i(\gamma_0, u)}{\tilde{S}^{(0)}(\gamma_0, u)}\alpha(H_i(\gamma, u))Y_i(u)\left(dH_0(u) + \gamma_0^T X_i(u)du\right) \xrightarrow{P} A(\gamma_0, t).$$

The predictable variation

$$< n^{1/2}\int_0^t J(u)\frac{dM(u)}{\tilde{S}^{(0)}(\gamma_0, u)} >= n\int_0^t J(s)\frac{S^{(0)}(\gamma_0, s)dH(S_0(s)) + S_*^{(0)}(\gamma_0, s)ds}{\tilde{S}^{(0)2}(\gamma_0, s)} \xrightarrow{P} \sigma_1^2(\gamma_0, t).$$

Let

$$H_{1i}(\gamma_0, u) = C(\gamma_0, t)\Sigma_1^{-1}(\gamma_0, \tau)H_i(\gamma_0, u) + nJ(u)/\tilde{S}^{(0)}(\gamma_0, u).$$

Then

$$\sqrt{n}[\tilde{H}_0(t) - H_0(t)] = n^{-1/2} \sum_{i=1}^{n} \int_0^t H_{1i}(\gamma_0, u) dM_i(u) + o_p(1).$$

By assumptions of the theorem for all $\varepsilon > 0$

$$\frac{1}{n} \sum_{i=1}^{n} \int_0^t H_{1i}^2(\gamma_0, u) I\{|H_{1i}(\gamma_0, u)| > \varepsilon\} Y_i(u) \alpha_i(u) du \xrightarrow{P} 0.$$

The asymptotic normality of $\sqrt{n}[\tilde{H}_0(t) - H_0(t)]$ follows from the theorem of Rebolledo. The proof of theorem 3 is complete.

■

Consider the asymptotic distribution of the estimator $\hat{S}_{x(\cdot)}$ of the survival function $S_{x(\cdot)}(t)$ under any covariate $x(\cdot)$. Denote

$$C_x(\gamma_0, t) = C(\gamma_0, t) + \int_0^t x^T(u) du, \quad g = G'.$$

Theorem 4. *Under assumptions of theorem 1*

$$\sqrt{n}[\hat{S}_{x(\cdot)}(t) - S_{x(\cdot)}(t)] \xrightarrow{D} N(0, \sigma_x^2) \quad as \quad n \to \infty,$$

where

$$\sigma_x^2(\gamma_0, t) = \{\sigma_1^2(\gamma_0, t) + C_x(\gamma_0, t)\Sigma_2(\gamma_0, \tau) C_x^T(\gamma_0, t) - 2C_x(\gamma_0, t)\Sigma_1^{-1}(\gamma_0, \tau) A(\gamma_0, t)\} g^2(H(S_x(t))).$$

Proof: By Taylor expansion around γ_0 we obtain (similarly as in the proof of theorem 3):

$$n^{1/2}[H(\hat{S}_{x(\cdot)}(t)) - H(S_{x(\cdot)}(t))] =$$
$$n^{1/2} \left\{ \tilde{H}_0(t, \gamma_0) - H_0(t) + \int_0^t x^T(u) du (\hat{\gamma} - \gamma_0) \right\} =$$
$$n^{1/2} \left\{ C_x(\gamma_0, t) \Sigma_1^{-1}(\gamma_0, t) U(\gamma_0, \tau) + \int_0^t J(u) \frac{dM(u)}{\tilde{S}^{(0)}(\gamma_0, u)}) + o_p(1) \right\}.$$

The proof of the asymptotical normality of $\sqrt{n}[H(\hat{S}_{x(\cdot)}(t)) - H(S_{x(\cdot)}(t))]$ is similar to the proof of the asymptotical normality of $\sqrt{n}[H(\hat{S}_0(t)) - H(S_0(t))]$ in the theorem 3. So we skip it. The asymptotical normality of $\sqrt{n}[\hat{S}_{x(\cdot)}(t) - S_{x(\cdot)}(t)]$ is obtained by the functional delta method. The proof is complete.

■

Remark 1. Replacing all the theoretical quantities by empirical ones in the theorems 1-4, we obtain consistent estimates for the limiting covariance matrice of $\sqrt{n}(\hat{\gamma}-\gamma_0)$ and the limiting variances of

$$\sqrt{n}(\tilde{H}_0(t)-H_0(t) \quad \text{and} \quad \sqrt{n}(\hat{S}_{X(\cdot)}(t)-S_{X(\cdot)}(t)).$$

□

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