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Testing absence of hazard rates crossing

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Abstract

A new flexible and simple semiparametric model, including the cases when hazard rates cross, go away, are proportional, approach or converge, is proposed. Semiparametric estimation procedures are given. A test for absence of hazard rates crossing is proposed. ***To cite this article: V. Bagdonavičius et al., C. R. Acad. Sci. Paris, Ser. I 347 (2009).***

Résumé

Test pour l'absence de croisement. Un modèle sémiparamétrique simple et flexible qui inclue des effets de croisement, d'éloignement, d'approchement, de proportionnalité et de convergence des fonctions de hasard est proposé. Des procédures d'estimation sémiparamétrique sont données. Un test pour l'absence de croisement est proposé. ***Pour citer cet article : V. Bagdonavičius et al., C. R. Acad. Sci. Paris, Ser. I 347 (2009).***

Version française abrégée

Si les fonctions de hasard ne se croisent pas on peut conclure que le risque de décès d'une population est plus petit que celui de la seconde population dans l'intervale de temps $[0, \infty)$. Donc une des populations est « uniformement plus fiable ». Parfois une telle hypothèse est plus intéresante à vérifier que celle de l'égalité des répartitions (l'hypothèse de homogeneité). Pour construire un test de l'absence de croisement nous proposons un modèle sémiparamétrique simple et flexible qui inclue non seulement l'effet de croisement mais aussi des effets d'éloignement, d'approchement, de proportionnalité et celui de convergence des fonctions de hasard. L'hypothèse de l'absence de croisement est une hypothèse sur les valeurs des paramètres de dimension finie de ce large modèle. Donc tout d'abord ce sont des procédures d'estimation qui sont discutées. D'autre part, ce problème d'estimation a son propre intérêt. Soit $\lambda(t|z)$ la fonction de hasard sous la covariable $z = (z_1, \ldots, z_s)^T$. On considère le modèle (6) qui a les propiétés mentionnées ci-dessus. On suppose que des données censurées à droite sont données par (9). Les paramètres θ peuvent être estimés en maximisant la fonction de vraisemblance modifiée (11) ou la fonction de vraisemblance non-paramétrique (12).

Posons $\delta = \beta\gamma$. On vérifie l'hypothèse

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$$H_0 : \delta \leqslant 0 \quad \text{contre l'alternative} \quad H_1 : \delta > 0. \tag{1}$$

L'hypothèse est equivalente à l'absence de croisement des fonctions de hasard. La loi limite de l'estimateur $\hat{\delta}$ est donnée par (14) et le test est basé sur la statistique $T = \sqrt{n}\,\hat{\delta}/\hat{\sigma}$; ici $\hat{\sigma}^2$ est l'estimateur consistant de la variance limite σ^2.

1. Introduction

When analyzing survival data from clinical trials, cross-effects of hazard rates are sometimes observed. A classical example is the well-known data of the Gastrointestinal Tumor Study Group, concerning effects of chemotherapy and radiotherapy on the survival times of gastric cancer patients (Stablein and Koutrouvelis [10], Klein and Moeschberger [8]). If the hazard rates of two populations do not cross then we can state that the risk of failure of one population is smaller than that of the second in time interval $[0, \infty)$. So one of populations is "uniformly more reliable". Such hypothesis sometimes is more interesting to verify then the hypothesis of the equality of distributions (homogeneity hypothesis). If, for example, the hypothesis is not true for two populations cured using usual and new treatment methods then it is possible that the new method gives better results only at the beginning of treatment and some measures must be undertaken before the crossing of hazard rates (changing of treatment methodology, etc.). Constructing tests for absence of hazard rate crossing we propose a new flexible and simple semiparametric model including not only possibility of hazard rates crossing but also most likely alternatives, stating that hazard rates go away, are proportional, approach or converge. The estimation problem has its own interest, too. Denote by $\lambda(t|z)$ the hazard rate of objects under possibly time varying and multi-dimensional covariate $z = (z_1, \ldots, z_s)^T$. If the problem of crossing of only two hazard rates is considered we can use one-dimensional constant in time dichotomous covariate z taking values 0 and 1 for the first and the second group of objects, respectively. Hsieh [7] considered the following model:

$$\lambda(t|z) = e^{\beta^z(t)+\gamma^T\tilde{z}(t)}\bigl\{\Lambda(t)\bigr\}^{e^{\gamma^T\tilde{z}(t)}-1}\lambda(t), \quad \Lambda(t) = \int_0^t \lambda(u)\,\mathrm{d}u, \tag{2}$$

λ is unknown baseline hazard rate, $\tilde{z} = (z_{i_1}, \ldots, z_{i_k})^T$, $1 \leqslant i_1 < \cdots < i_k \leqslant s$. This model does not contain interesting alternatives to crossing: the hazards rates under different constant covariates cross for any values of the parameters β and $\gamma \neq 0$. In two sample problem denote by $\lambda_i(t)$ and $\Lambda_i(t)$ the hazard rate and the cumulative hazard, respectively, of the ith group of objects, $i = 1, 2$, and $c(t) = \lambda_2(t)/\lambda_1(t)$ – their ratio. The model of Hsieh implies that $c(t) = \{\Lambda(t)\}^{e^\gamma - 1}$ is monotone, $c(0) = 0$, $c(\infty) = \infty$ or *vice versa*, so there exists the point t_0: $c(t_0) = 1$. If $\gamma = 0$ then the hazard rates coincide. Bagdonavičius and Nikulin proposed in [3] more versatile model including not only crossing but also going away hazard rates:

$$\lambda(t|z) = e^{\beta^T z(t)}\bigl\{1 + \Lambda(t|z)\bigr\}^{1-e^{\gamma^T z(t)}}\lambda(t), \quad \Lambda(t|z) = \int_0^t \lambda(u|z)\,\mathrm{d}u. \tag{3}$$

In two sample problem the ratio $c(t) = e^\beta\{1 + e^{\beta+\gamma}\Lambda(t)\}^{e^{-\gamma}-1}$ is monotone, $c(0) = e^\beta$, $c(\infty) = \infty$ if $\gamma < 0$ and $c(\infty) = 0$ if $\gamma > 0$. So the hazard rates may cross or go away but cannot converge or approach (in sense of the ratio $c(t)$). To obtain richer class of alternatives Zeng and Lin [12] include an additional parameter to the above mentioned models: in terms of cumulative hazards their models are written (a subset $\tilde{z}$ of z is supposed to be constant in time) respectively

$$\Lambda(t|z) = G\Biggl(\biggl(\int_0^t e^{\beta^T z(u)}\,\mathrm{d}\Lambda(u)\biggr)^{e^{\gamma^T\tilde{z}}}\Biggr) \quad \text{and} \quad \Lambda(t|z) = G\Biggl(\biggl(1 + \int_0^t e^{\beta^T z(u)}\,\mathrm{d}\Lambda(u)\biggr)^{e^{\gamma^T\tilde{z}}}\Biggr) - G(1); \tag{4}$$

here

$$G(x) = \frac{(1+x)^\rho - 1}{\rho}, \quad \rho > 0, \qquad G(x) = \log(1+x), \quad \rho = 0 \tag{5}$$

(Box–Cox transformation) or

$$G(x) = \frac{\log(1+rx)}{r}, \quad r > 0, \qquad G(x) = x, \quad r = 0. \tag{5'}$$

Taking $G(x) = x$, the models of Hsieh and Bagdonavičius and Nikulin are obtained from (4).

Henderson [6] remarks that it is difficult to see the role of three parameters in these models. The estimation procedure in such general models is also very complicated.

We propose a general model including crossing of hazard rates and wide class of alternatives of non-intersecting hazard rates which cannot only go away but also to approach. This model does not contain additional parameter ρ or r given in (5) and (5′). The model will be used for construction of a test for absence of crossing of hazard rates of two populations. For this purpose only dichotomous univariate covariate is needed. Nevertheless, we give estimation procedures in more general case, too.

2. Modeling

We propose the model:

$$\lambda(t|z) = \frac{e^{\beta^T z(t) + \Lambda(t) e^{\gamma^T \tilde{z}(t)}}}{1 + e^{\beta^T z(t) + \gamma^T \tilde{z}(t)}[e^{\Lambda(t) e^{\gamma^T \tilde{z}(t)}} - 1]} \lambda(t), \quad \Lambda(t) = \int_0^t \lambda(u)\,\mathrm{d}u; \tag{6}$$

λ is unknown baseline hazard rate; $\tilde{z} = (z_{i_1}, \ldots, z_{i_k})^T$, $1 \leqslant i_1 < \cdots < i_k \leqslant s$, is a subset of $z = (z_1, \ldots, z_s)^T$.

Set

$$\theta = (\beta^T, \gamma^T)^T, \qquad g(x, z, \theta) = \frac{e^{\beta^T z + x e^{\gamma^T \tilde{z}}}}{1 + e^{\beta^T z + \gamma^T \tilde{z}}[e^{x e^{\gamma^T \tilde{z}}} - 1]}. \tag{7}$$

Taking into consideration that the purpose of the Note is to construct a test for absence of crossing of hazard rates of two populations, let us compare the hazard rates of two groups which correspond to values 0 and 1 of dichotomous covariate z. In this particular case $\tilde{z} = z$. Note that

$$\lambda_1(t) = \lambda(t|0) = \lambda(t), \quad \lambda_2(t) = \lambda(t|1) = g[\Lambda(t), 1, \theta]\lambda(t), \quad c(t) = \lambda(t|1)/\lambda(t|0) = g[\Lambda(t), 1, \theta]. \tag{8}$$

The ratio of hazard rates $c(t)$ is monotone and $c(0) = e^{\beta}$, $c(\infty) = e^{-\gamma}$. So e^{β} shows the value the ratio of hazard rates at the beginning of life and $e^{-\gamma}$ – at the end.

In dependence of the values of the parameters β and γ the ratio $c(t)$ has the following properties:

1) If $\beta > 0, \gamma > 0$ then it decreases from $e^{\beta} > 1$ to $e^{-\gamma} \in (0, 1)$, so the hazard rates of two populations cross in the interval $(0, \infty)$.
2) If $\beta < 0, \gamma < 0$ then it increases from $e^{\beta} \in (0, 1)$ to $e^{-\gamma} > 1$, so the hazard rates cross in the interval $(0, \infty)$.
3) If $\beta > 0, \gamma < 0, \beta + \gamma > 0$, then it decreases from $e^{\beta} > 1$ to $e^{-\gamma} > 1$, so the hazard rates do not cross.
4) If $\beta > 0, \gamma < 0, \beta + \gamma < 0$, then it increases from $e^{\beta} > 1$ to $e^{-\gamma} > 1$, so the hazard rates do not cross.
5) If $\beta < 0, \gamma > 0, \beta + \gamma > 0$, then it decreases from $e^{\beta} \in (0, 1)$ to $e^{-\gamma} \in (0, 1)$, so the hazard rates do not cross.
6) If $\beta < 0, \gamma > 0, \beta + \gamma < 0$, then it increases from $e^{\beta} \in (0, 1)$ to $e^{-\gamma} \in (0, 1)$, so the hazard rates do not cross.
7) If $\beta = -\gamma$ then the ratio is constant as in the Cox model.
8) If $\gamma = 0, \beta > 0$ then the ratio decreases from $e^{\beta} > 1$ to 1, so the hazard rates meet at infinity.
9) If $\gamma = 0, \beta < 0$ then the ratio increases from $e^{\beta} \in (0, 1)$ to 1, so the hazard rates meet at infinity.
10) If $\gamma > 0, \beta = 0$ then the ratio decreases from 1 to $e^{-\gamma} \in (0, 1)$.
11) If $\gamma < 0, \beta = 0$ then the ratio increases from 1 to $e^{-\gamma} > 1$.
12) If $\gamma = \beta = 0$ then the hazard rates coincide.

So the hazard rates may cross, approach, go away, be proportional, or coincide.

If $\beta\gamma > 0$ then not only hazard rates but also the survival functions cross. Indeed, in such a case the hazard rates cross at the point

$$t_0 = \Lambda^{-1}\left(e^{-\gamma} \ln \frac{1 - e^{\gamma+\beta}}{e^{\beta} - e^{\gamma+\beta}}\right) > 0.$$

If $\beta > 0, \gamma > 0$ (or $\beta < 0, \gamma < 0$) then the difference $\lambda_2(t) - \lambda_1(t)$ is positive (negative) in $(0, t_0)$ and negative (positive) in (t_0, ∞), so the difference of cumulative hazards $\Lambda_2(t) - \Lambda_1(t)$ has $\cup$ ($\cap$) form. Taking into account that $\Lambda_2(0) - \Lambda_1(0) = 0$, $\lim_{t\to\infty}(\Lambda_2(t) - \Lambda_1(t)) = -\infty$ $(+\infty)$ we obtain that the cumulative hazards and the survival functions cross in some point $t_1 \in (t_0, \infty)$.

3. Semiparametric estimation

Suppose that n objects are observed. The ith from them is observed under the covariate z_i.

Denote by T_i and C_i the failure and censoring times for the ith object, and set

$$X_i = \min(T_i, C_i), \quad \delta_i = \mathbf{1}_{\{T_i \leqslant C_i\}}, \quad N_i(t) = \mathbf{1}_{\{T_i \leqslant t, \delta_i = 1\}},$$
$$Y_i(t) = \mathbf{1}_{\{X_i \geqslant t\}}, \quad N = \sum_{j=1}^{n} N_i, \quad Y = \sum_{i=1}^{n} Y_i; \tag{9}$$

$\mathbf{1}_A$ denotes the indicator of the event A. The data consists of $(N_i(t), Y_i(t), z_i(t); t \in [0, \tau])$, τ is a constant.

3.1. Modified partial likelihood estimators

At first we give for the model (6) the partial likelihood function $L(\theta)$ (see Andersen et al. [1]):

$$L(\theta) = \prod_{i=1}^{n}\left[\int_0^{\tau} \frac{g(\Lambda(u), z_i(t), \theta)}{S^{(0)}(u, \Lambda, \theta)}\, \mathrm{d}N_i(u)\right]^{\delta_i} \quad \text{with } S^{(0)}(u, \Lambda, \theta) = \sum_{i=1}^{n} Y_i(u) g\big(\Lambda(u), z_i(u), \theta\big), \tag{10}$$

depends on the unknown cumulative hazard Λ. So differently from the proportional hazards (Cox) model it cannot be directly used for estimation of θ. We use the modified partial likelihood (MPL) method introduced by Bagdonavičius and Nikulin [2] for generalized proportional hazards models and generalized for the model with crossing survival functions (3). Tests for proportional hazards and also for homogeneity against crossing of hazard rates alternative (Bagdonavičius et al. [3,4]) were constructed using the MPL estimators. They are more powerful than all well-known tests. In the case of constant in time covariates Dabrowska [5] studied asymptotic properties of MPL estimators for the model $\Lambda(t|z) = A(\Lambda(t), \theta|z)$, which is generalization of the model (6). The MPL estimators for the model (6) are constructed as follows. The function Λ is replaced in (10) by the "estimator" $\tilde{\Lambda}$ (depending on θ) which is defined recurrently from the equation

$$\tilde{\Lambda}(t, \theta) = \int_0^{t} \frac{\mathrm{d}N(u)}{S^{(0)}(u-, \tilde{\Lambda}, \theta)}.$$

This "estimator" is obtained using the martingale property of the $N_i - \int Y_i\, \mathrm{d}\Lambda_i$. The modified likelihood function is

$$\tilde{L}(\theta) = \prod_{j=1}^{n}\left[\int_0^{\tau} \frac{g(\tilde{\Lambda}(u, \theta), z_i(u), \theta)}{S^{(0)}(u, \tilde{\Lambda}, \theta)}\, \mathrm{d}N_i(u)\right]^{\delta_i}. \tag{11}$$

For fixed θ computing of modified loglikelihood function is simple. Let $T_1^* < \cdots < T_r^*$ be observed and ordered distinct failure times of unified data, $r \leqslant n$. Note by d_j the number of observed failures of the objects at the moment T_j^*. Then the modified loglikelihood function is

$$\tilde{\ell}(\theta) = \sum_{j=1}^{r} \sum_{l=1}^{d_j} \big\{\ln g\big(\tilde{\Lambda}\big(T_j^*, z_{(jl)}, \theta\big), \theta\big) - \ln S^{(0)}\big(T_j^*, \tilde{\Lambda}, \theta\big)\big\};$$

here (jl) is the index of the lth object failed at the moment T_j^*, $l = 1, \ldots, d_j$.

The values of the functions $\tilde{\Lambda}$ and $S^{(0)}$ are computed recurrently:

$$\tilde{\Lambda}(0;\theta)=0,\quad S^{(0)}(0,\tilde{\Lambda},\theta)=\sum_{j=1}^{n}Y_j(0)g\big(\tilde{\Lambda}(0;\theta),z_j(0),\theta\big)=\sum_{j=1}^{n}e^{\beta^T z_j(0)},\quad \tilde{\Lambda}\big(T_1^*;\theta\big)=\frac{d_1}{S^{(0)}(0,\tilde{\Lambda},\theta)},$$

$$S^{(0)}\big(T_1^*,\tilde{\Lambda},\theta\big)=\sum_{j=1}^{n}Y_j\big(T_1^*\big)g\big(\tilde{\Lambda}\big(T_1^*;\theta\big),z_j\big(T_1^*\big),\theta\big),\quad \tilde{\Lambda}\big(T_j^*;\theta\big)=\tilde{\Lambda}\big(T_{j-1}^*;\theta\big)+\frac{d_j}{S^{(0)}(T_{j-1}^*,\tilde{\Lambda},\theta)},$$

$$S^{(0)}\big(T_j^*,\tilde{\Lambda},\theta\big)=\sum_{i=1}^{n}Y_i\big(T_j^*\big)g\big(\tilde{\Lambda}\big(T_j^*;\theta\big),z_i\big(T_j^*\big),\theta\big)\quad (j=2,\dots,r).$$

The initial value $\theta_0=(\beta_0,1)$, where β_0 as an estimator of β using the PH model, may be chosen.

3.2. Nonparametric maximum likelihood estimators

The non-parametric likelihood function $L=L(\theta,\lambda_1,\dots,\lambda_m)$ (NPLF, Zeng and Lin [11,12]), which is parametric in fact for any fixed n, has the form

$$L=\prod_{i=1}^{n}\prod_{t\leqslant\tau}\big[\lambda_{\{-\}}(t)g\big(\Lambda_{\{-\}}(t),z_i,\theta\big)\big]^{\mathrm{d}N_i(t)}\exp\Bigg\{-\int_0^\tau Y_i(u)g\big(\Lambda_{\{-\}}(u),z_i,\theta\big)\,\mathrm{d}\Lambda_{\{-\}}(u)\Bigg\}\tag{12}$$

here $\Lambda_{\{-\}}(t)$ is the step function with the jumps λ_j at the points T_j^*, $j=1,\dots,m$, $\Lambda_{\{-\}}(0)=0$, and $\lambda_{\{-\}}(T_j^*)=\lambda_j$. NPLF is a modification of the parametric likelihood function (PLF) for θ with known λ (PLF contains the known values λ_j of the hazard function λ only at the points T_j^*) considering λ_j as unknown parameters and replacing $\Lambda(t)$ by the step function $\Lambda_{\{-\}}(t)$. The log-likelihood function is

$$\ell(\theta,\lambda_1,\dots,\lambda_m)=\sum_{j=1}^{m}\sum_{s=1}^{d_j}\Bigg[\ln\lambda_j+\ln g\Bigg(\sum_{l=1}^{j}\lambda_l,z_{(js)},\theta\Bigg)\Bigg]-\sum_{i=1}^{n}\sum_{j=1}^{m}Y_i\big(T_j^*\big)\lambda_j g\Bigg(\sum_{l=1}^{j}\lambda_l,z_i,\theta\Bigg).$$

The estimators $\hat{\theta}$, $\hat{\lambda}_j$ of the parameters θ and λ_j can be computed using the backward recursive method given in Zeng and Lin [12]. The non-parametric likelihood function L can be written as the particular case of the model

$$L=\prod_{i=1}^{n}\prod_{t\leqslant\tau}\lambda_{\{-\}}^{\mathrm{d}N_i(t)}(t)\Psi(O_i;\theta,\Lambda_{\{-\}}),\tag{13}$$

taking

$$\Psi(O_i;\theta,\Lambda_{\{-\}})=\prod_{t\leqslant\tau}\big[g\big(\Lambda_{\{-\}}(t),z_i,\theta\big)\big]^{\mathrm{d}N_i(t)}\exp\Bigg\{-\int_0^\tau Y_i(u)g\big(\Lambda_{\{-\}}(u),z_i,\theta\big)\,\mathrm{d}\Lambda_{\{-\}}(u)\Bigg\};$$

here O_i pertains to the observation of the ith object. Zeng and Lin [11,12] give the regularity conditions (C1)–(C8) for the model (13), Under these regularity conditions $\hat{\theta}\xrightarrow{P}\theta$, $\sqrt{n}(\hat{\theta}-\theta)\xrightarrow{d}N_{k+s}(0,\Sigma)$, and the limiting covariance matrix $\Sigma=\|\sigma_{ij}\|$ attains the semiparametric efficiency bound.

Let us consider the case of constant in time covariates. Sufficient for the regularity conditions (C1)–(C8) to be true for the model (6) are the following conditions:

1) The true parameter value θ_0 belongs to the interior of a compact set $\Theta\subset\mathbf{R}^{k+s}$, and $\lambda(t)>0$ for all $t\in[0,\tau]$.
2) $(N_i(t),Y_i(t),z_i;t\in[0,\tau])$, $i=1,\dots,n$, are i.i.d. and z_i can take more than one value with positive probabilities.
3) With probability one, $P(C_i\geqslant\tau|z_i)>\delta_0>0$ for some constant δ_0.

In the case of the model (3), i.e. when $g(x,z,\theta)=e^{\beta^T z(t)}\{1+\Lambda(t|z)\}^{1-e^{\gamma^T z(t)}}$, this is proved in Zeng and Lin [11,12]. In the case of the model (6) with the function $g(x,z,\theta)$ given by (7), the proof is practically the same.

4. Testing for the absence of crossing

Now we are ready to construct a test for absence of hazard rate crossing. To do this we use above considered estimators in the partial case of dichotomous covariate with values 0 and 1, corresponding to two populations. Both parameters β and γ are scalar in this case. Set $\delta = \beta\gamma$. We test the hypothesis

$$H_0\colon\ \delta \leqslant 0 \quad \text{against the alternative} \quad H_1\colon\ \delta > 0. \tag{14}$$

The hypothesis means that the hazard rates do not cross and the alternative means that the hazard rates cross. If $\delta \neq 0$ then by delta method $\sqrt{n}(\hat{\delta} - \delta) \xrightarrow{d} N(0, \sigma^2)$, where $\sigma^2 = \gamma^2\sigma_{11} + 2\beta\gamma\sigma_{12} + \beta^2\sigma_{22}$.

Let $pl(\theta) = \max_{\Lambda}[\ell(\theta, \Lambda)]$ be the profile likelihood (Murphy and Van der Vaart [9]). Denote by $\Sigma^{-1} = \|\sigma^{ij}\|$ the inverse of the covariance matrix Σ. Then under regularity conditions (see Zeng and Lin [11,12]) for any $v = (v_1, v_2)^T \in \mathbf{R}^2$ and any $c \in \mathbf{R}$

$$\frac{1}{n\varepsilon_n}\big[2pl(\hat{\beta}, \hat{\gamma}) - pl(\hat{\beta} + \varepsilon_n v_1, \hat{\gamma} + \varepsilon_n v_2) - pl(\hat{\beta} - \varepsilon_n v_1, \hat{\gamma} - \varepsilon_n v_2)\big] \xrightarrow{P} v^T \Sigma^{-1} v;$$

here $\varepsilon_n = c/\sqrt{n}$. So for any $c \in \mathbf{R}$ the estimators

$$\hat{\sigma}^{11} = \frac{1}{n\varepsilon_n^2}\big[2pl(\hat{\beta}, \hat{\gamma}) - pl(\hat{\beta} + \varepsilon_n, \hat{\gamma}) - pl(\hat{\beta} - \varepsilon_n, \hat{\gamma})\big],$$
$$\hat{\sigma}^{22} = \frac{1}{n\varepsilon_n^2}\big[2pl(\hat{\beta}, \hat{\gamma}) - pl(\hat{\beta}, \hat{\gamma} + \varepsilon_n) - pl(\hat{\beta}, \hat{\gamma} - \varepsilon_n)\big],$$
$$\hat{\sigma}^{12} = \frac{1}{2}\left(\hat{\sigma}^{11} + \hat{\sigma}^{22} - \frac{1}{n\varepsilon_n^2}\big[2pl(\hat{\beta}, \hat{\gamma}) - pl(\hat{\beta} + \varepsilon_n, \hat{\gamma} - \varepsilon_n) - pl(\hat{\beta} - \varepsilon_n, \hat{\gamma} + \varepsilon_n)\big]\right)$$

are consistent. Consistent estimators $\hat{\sigma}_{ij}$ of the parameters σ_{ij} are obtained take the inverse of the estimated matrix $\hat{\Sigma}^{-1} = \|\hat{\sigma}^{ij}\|$. The test statistic has the form $T = \sqrt{n}\hat{\delta}/\hat{\sigma}$, where $\hat{\sigma}^2 = \hat{\gamma}^2\hat{\sigma}_{11} + 2\hat{\beta}\hat{\gamma}\hat{\sigma}_{12} + \hat{\beta}^2\hat{\sigma}_{22}$. The hypothesis is rejected if $T > z_\alpha$; z_α is the upper α-quantile of the standard normal distribution.

Alternative and simpler way is to use the bootstrap estimator of the limit variance σ^2 using modified partial likelihood estimators of β and γ. Note that under homogeneity hypothesis $H_0\colon \beta = \gamma = 0$ the test statistic is degenerated because in such a case the limit variance σ^2 is zero. So before using the proposed test the homogeneity hypothesis $H_0\colon \beta = \gamma = 0$ must be verified. Only if this hypothesis is rejected then the test for absence of hazard rates crossing may be used.

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