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ASYMPTOTIC ANALYSIS OF A NEW DYNAMIC SEMIPARAMETRIC REGRESSION MODEL WITH CROSS-EFFECTS OF SURVIVALS

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 for censored data are given. A test for absence of hazard rates crossing is proposed.

I. Introduction

When analyzing survival data from clinical trials, cross-effects of survival functions 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], Bagdonavičius, Kruopis and Nikulin [2]).

If the hazard rates of two populations do not cross then we can state that the risk of failure of one population is smaller then 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.).

Denote by $\lambda(t|z)$ the hazard rate of objects under possibly time varying and multi-dimensional covariate $z = (z_1, \dots, z_s)^T$.

For solution of two hazard rates crossing problem we can use one-dimensional constant in time dichotomous covariate z. In such a case, we

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can suppose that the covariate z takes the values 0 and 1 for the first and the second group of objects, respectively.

Denote by $\lambda_i(t)$ and $\Lambda_i(t) = \int_0^t \lambda_i(u)du$ the hazard rate and the cumulative hazard, respectively, of the ith group of objects, $i = 1, 2$, and

$$c(t) = \frac{\lambda_2(t)}{\lambda_1(t)}. \tag{1}$$

Hsieh [7] considered the following model:

$$\lambda(t|z) = e^{\beta^T z(t) + \gamma^T \widetilde{z}(t)} \{\Lambda(t)\}^{e^{\gamma^T \widetilde{z}(t)} - 1} \lambda(t), \quad \Lambda(t) = \int_0^t \lambda(u)du, \tag{2}$$

λ is unknown baseline hazard rate, $\widetilde{z} = (z_{i_1}, \ldots, z_{i_k})^T$, $1 \leqslant i_1 < \cdots < i_k \leqslant s$.

The model of Hsieh 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 the ratio

$$c(t) = \{\Lambda(t)\}^{e^{\gamma} - 1}.$$

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, Hafdi and Nikulin [3], see also Bagdonavičius and Nikulin [4], considered more versatile model including not only crossing but also going away hazard rates:

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

If z is constant in time then resolving the differential equation (3) with respect to $\Lambda(t|z)$ and taking the derivative of it the model can be written in the explicit form

$$\lambda(t|z) = e^{\beta^T z} \left\{1 + e^{(\beta+\gamma)^T z} \Lambda(t)\right\}^{e^{-\gamma^T z} - 1} \lambda(t), \tag{4}$$

where $\Lambda(t) = \int_0^t \lambda(u)du$ is the baseline cumulative hazard.

In two sample problem the ratio

$$c(t) = e^{\beta} \left\{1 + e^{\beta+\gamma}\Lambda(t)\right\}^{e^{-\gamma}-1}$$

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 can not converge or approach (in sense of the ratio $c(t)$).

To obtain richer class of alternatives Zeng and Lin [11] include additional parameter to above mentioned models: in terms of cumulative hazards their models are written ($\widetilde{z}$ is supposed to be constant in time), respectively,

$$\Lambda(t|z) = G\left(\left(\int_0^t e^{\beta^T z(u)} d\Lambda(u)\right)^{e^{\gamma^T \widetilde{z}}}\right) \tag{5}$$

and

$$\Lambda(t|z) = G\left(\left(1 + \int_0^t e^{\beta^T z(u)} d\Lambda(u)\right)^{e^{\gamma^T \widetilde{z}}}\right) - G(1); \tag{6}$$

here

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

(Box-Cox transformation) or

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

Taking $G(x) = x$ the models of Hsieh [7] and Bagdonavičius and Nikulin [4] are obtained.

Henderson [6] remarks that it is difficult to see the role of three parameters in these models. 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 can not only go away but also to approach. This model does not contain additional parameters (as ρ or r).

2. The model

The model:

$$\lambda(t|z) = \frac{e^{\beta^T z(t) + \Lambda(t) e^{\gamma^T \widetilde{z}(t)}}}{1 + e^{\beta^T z(t) + \gamma^T \widetilde{z}(t)} [e^{\Lambda(t) e^{\gamma^T \widetilde{z}(t)}} - 1]} \lambda(t), \quad \Lambda(t) = \int_0^t \lambda(u) du, \tag{7}$$

λ is unknown baseline hazard rate.

Set

$$\theta = (\beta^T, \gamma^T)^T, \quad g(x, z, \theta) = \frac{e^{\beta^T z + x e^{\gamma^T \widetilde{z}}}}{1 + e^{\beta^T z + \gamma^T \widetilde{z}} [e^{x e^{\gamma^T \widetilde{z}}} - 1]}. \tag{8}$$

In the case of two hazard rates crossing problem $\widetilde{z} = z$. Note that

$$\lambda_1(t) = g[\Lambda(t), 0, \theta] \, \lambda(t) = \lambda(t), \quad \lambda_2(t) = g[\Lambda(t), 1, \theta] \, \lambda(t),$$

$$c(t) = g[\Lambda(t), 1, \theta]. \tag{9}$$

If the model (7) is used then the ratio of hazard rates $c(t)$ is monotone and

$$c(0) = e^{\beta}, \quad c(\infty) = e^{-\gamma}.$$

So e^{β} shows the value of 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 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, 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 $\Lambda_2(0) - \Lambda_1(0) = 0$, $\lim\limits_{t\to\infty} (\Lambda_2(t) - \Lambda_1(t)) = -\infty$ $(+\infty)$ we obtain that the cumulative hazards and the survival functions cross in some point $t_1 \in (t_0, \infty)$.

3. 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

$$X_i = \min(T_i, C_i), \quad \delta_i = \mathbf{1}_{\{T_i \leqslant C_i\}},$$

$$N_i(t) = \mathbf{1}_{\{T_i \leqslant t, \delta_i = 1\}}, \quad Y_i(t) = \mathbf{1}_{\{X_i \geqslant t\}};$$

here $\mathbf{1}_A$ denotes the indicator of the event A.

Set $N(t) = \sum\limits_{j=1}^{n} N_i(t)$ and $Y(t) = \sum\limits_{i=1}^{n} Y_i(t)$.

3.1. Modified partial likelihood estimators

At first we propose simple estimators of the unknown parameters which are not fully efficient (but very good in the case of finite samples) and can be used as initial estimators. Possession of such estimators is very important because efficient non-parametric maximum likelihood estimators are complicated.

According to the definition of Andersen, Borgan, Gill, and Keiding [1], the partial likelihood function is

$$L(\theta) = \prod_{i=1}^{n} \left[\int_0^\infty \frac{g(\Lambda(v), z_i(t), \theta)}{S^{(0)}(u, \Lambda, \theta)} \, dN_i(v) \right]^{\delta_i}, \tag{10}$$

where

$$S^{(0)}(u, \Lambda, \theta) = \sum_{i=1}^{n} Y_i(u) g(\Lambda(u), z_i(u), \theta).$$

One can see that $L(\theta)$ depends on the unknown cumulative hazard Λ. It is very natural, see Bagdonavičius and Nikulin [5], to replace it by its "pseudo-estimator" $\widetilde{\Lambda}$ (still depending on θ) which is defined recurrently from the equation:

$$\widetilde{\Lambda}(t, \theta) = \int_0^t \frac{dN(u)}{S^{(0)}(u-, \widetilde{\Lambda}, \theta)}.$$

This "estimator" is obtained using the martingale property of the $N_i - \int Y_i d\Lambda_i$.

So, according Bagdonavičius and Nikulin [5], we consider the *modified likelihood function*

$$\widetilde{L}(\theta) = \prod_{j=1}^{n} \left[\int_0^\infty \frac{g(\widetilde{\Lambda}(u, \theta), z_i(u), \theta)}{S^{(0)}(u, \widetilde{\Lambda}, \theta)} \, dN_i(u) \right]^{\delta_i}.$$

We use Splus program and the general quasi-Newton optimization algorithm seeking the value of θ which maximizes the modified partial likelihood (MPL) function with respect to θ.

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

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

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

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

$$\widetilde{\Lambda}(0;\theta) = 0, \quad S^{(0)}(0, \widetilde{\Lambda}, \theta) = \sum_{j=1}^{n} Y_j(0) g(\widetilde{\Lambda}(0;\theta), z_j(0), \theta) = \sum_{j=1}^{n} e^{\beta^T z_j(0)},$$

$$\widetilde{\Lambda}(T_1^*;\theta) = \frac{d_1}{S^{(0)}(0, \widetilde{\Lambda}, \theta)},$$

$$S^{(0)}(T_1^*, \widetilde{\Lambda}, \theta) = \sum_{j=1}^{n} Y_j(T_1^*) g(\widetilde{\Lambda}(T_1^*;\theta), z_j(T_1^*), \theta),$$

$$\widetilde{\Lambda}(T_j^*;\theta) = \widetilde{\Lambda}(T_{j-1}^*;\theta) + \frac{d_j}{S^{(0)}(T_{j-1}^*, \widetilde{\Lambda}, \theta)},$$

$$S^{(0)}(T_j^*, \widetilde{\Lambda}, \theta) = \sum_{j=1}^{n} Y_j(T_j^*) g(\widetilde{\Lambda}(T_j^*;\theta), z_j(T_j^*), \theta) \quad (j = 2, \dots, r).$$

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 nonparametric likelihood function (NPLF, Zeng and Lin [11]), which is parametric in fact for any fixed n, has the form

$$L(\theta, \lambda_1, \dots, \lambda_m) = \prod_{i=1}^{n} \prod_{t \leqslant \tau} \big[\lambda_{\{-\}}(t) g(\Lambda_{\{-\}}(t), z_i, \theta) \big]^{dN_i(t)}$$

$$\exp\left\{ - \int_0^\tau Y_i(u) g(\Lambda_{\{-\}}(u), z_i, \theta) d\Lambda_{\{-\}}(u) \right\}$$

$$= \prod_{j=1}^{m} \prod_{s=1}^{d_j} \lambda_j g\Big(\sum_{l=1}^{j} \lambda_l, z_{(jl)}, \theta \Big) \exp\Big\{ - \sum_{i=1}^{n} \sum_{j=1}^{m} Y_i(T_j^*) \lambda_j g(\sum_{l=1}^{j} \lambda_l, z_i, \theta) \Big\};$$

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

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

The estimators $\widehat{\theta}$, $\widehat{\lambda}_j$ of the parameters θ and λ_j can be computed using the backward recursive method given in Zeng and Lin [11]. In the considered case of NPLF, this method gives the following formulas.

Set $\alpha = \sum_{j=1}^{m} \lambda_j$, $h_j = \lambda_j / \alpha$, $\sum_{j=1}^{m} h_j = 1$. We have

$$(\ell)'_{\lambda_m} = \frac{d_m}{\lambda_m} + \sum_{s=1}^{d_m} (\ln g)'_1 \Big(\sum_{l=1}^{m} \lambda_l, z_{(ms)}, \theta \Big) - \sum_{i=1}^{n} Y_i(T_m^*) g\Big(\sum_{l=1}^{m} \lambda_l, z_i, \theta \Big) - \lambda_m \sum_{i=1}^{n} Y_i(T_m^*) g'_1 \Big(\sum_{l=1}^{m} \lambda_l, z_i, \theta \Big) = \frac{d_m}{\alpha h_m} + \sum_{s=1}^{d_m} (\ln g)'_1 (\alpha, z_{(ms)}, \theta) - \sum_{i=1}^{n} Y_i(T_m^*) g(\alpha, z_i, \theta) - \alpha h_m \sum_{i=1}^{n} Y_i(T_m^*) g'_1(\alpha, z_i, \theta) = 0,$$

$$g'_1(x, z, \theta) = \frac{e^{\beta^T z + \gamma^T \widetilde{z} + x e^{\gamma^T \widetilde{z}}} [1 - e^{\beta^T z + \gamma^T \widetilde{z}}]}{[1 + e^{\beta^T z + \gamma^T \widetilde{z}} (e^{x e^{\gamma^T \widetilde{z}}} - 1)]^2},$$

$$(\ln g)'_1 (x, z, \theta) = \frac{e^{\gamma^T \widetilde{z}} [1 - e^{\beta^T z + \gamma^T \widetilde{z}}]}{1 + e^{\beta^T z + \gamma^T \widetilde{z}} (e^{x e^{\gamma^T \widetilde{z}}} - 1)}.$$

$$
\begin{aligned}
(\ell)'_{\lambda_k} - (\ell)'_{\lambda_{k+1}} = \frac{d_k}{\alpha h_k} - \frac{d_{k+1}}{\alpha h_{k+1}} &+ \sum_{s=1}^{d_k} (\ln g)'_1 \Big(\alpha \Big(1 - \sum_{l=k+1}^{m} h_l \Big), z_{(ks)}, \theta \Big) \\
&- \sum_{i=1}^{n} \Big[Y_i(T_k^*) g \Big(\alpha \Big(1 - \sum_{l=k+1}^{m} h_l \Big), z_i, \theta \Big) \\
&- Y_i(T_{k+1}^*) g \Big(\alpha \Big(1 - \sum_{l=k+2}^{m} h_l \Big), z_i, \theta \Big) \mathbb{1}_{\{k<m-1\}} \Big] \\
&- \alpha h_k \sum_{i=1}^{n} Y_i(T_k^*) g'_1 \Big(\alpha \Big(1 - \sum_{l=k+1}^{m} h_l \Big), z_i, \theta \Big) = 0.
\end{aligned}
$$

So, if θ, α are fixed then the parameter $h_m \in (0,1)$ verifies the equation

$$
\begin{aligned}
&\alpha^2 h_m^2 \sum_{i=1}^{n} Y_i(T_m^*) g'_1(\alpha, z_i, \theta) \\
&\quad - \alpha h_m \Big\{ \sum_{s=1}^{d_m} (\ln g)'_1(\alpha, z_{(ms)}, \theta) - \sum_{i=1}^{n} Y_i(T_m^*) g(\alpha, z_i, \theta) \Big\} - d_m = 0,
\end{aligned}
$$

and $h_k \in (0,1)$ $(1 \leqslant k < m)$ are computed recursively from the equations

$$
\begin{aligned}
&\alpha^2 h_k^2 \sum_{i=1}^{n} Y_i(T_k^*) g'_1 \Big(\alpha \Big(1 - \sum_{l=k+1}^{m} h_l \Big), z_i, \theta \Big) \\
&\quad + \alpha h_k \Big\{ - \frac{d_{k+1}}{\alpha h_{k+1}} + \sum_{s=1}^{d_k} (\ln g)'_1 \Big(\alpha \Big(1 - \sum_{l=k+1}^{m} h_l \Big), z_{(ks)}, \theta \Big) \\
&\quad - \sum_{i=1}^{n} \Big[Y_i(T_k^*) g \Big(\alpha \Big(1 - \sum_{l=k+1}^{m} h_l \Big), z_i, \theta \Big) \\
&\quad - Y_i(T_{k+1}^*) g \Big(\alpha \Big(1 - \sum_{l=k+2}^{m} h_l \Big), z_i, \theta \Big) \mathbb{1}_{\{k<m-1\}} \Big] \Big\} + d_k = 0.
\end{aligned}
$$

So $h_k = h_k(\alpha, \theta)$. For given θ the parameter α verifies the equation $\sum_{i=1}^{m} h_k(\alpha, \theta) = 1$.

Under simple regularity conditions which are very similar to the conditions written to the model (7) (see Zeng and Lin [11])

$$
\widehat{\theta} \xrightarrow{P} \theta, \quad \sqrt{n}(\widehat{\theta} - \theta) \xrightarrow{d} N_2(0, \Sigma),
$$

and the limiting covariance matrix $\Sigma = ||\sigma_{ij}||$ attains the semiparametric efficiency bound.

4. The text

Set $\gamma = \beta\gamma$. We test the hypothesis

$$H_0 : \gamma \leqslant 0 \quad \text{against the alternative} \quad H_1 : \gamma > 0.$$

The hypothesis means that the hazard rates do not cross and the alternative means that the hazard rates cross.

By delta method

$$\sqrt{n}(\widehat{\gamma} - \gamma) \xrightarrow{d} N(0, \sigma^2),$$

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]) for any $v = (v_1, v_2)^T \in \mathbf{R}^2$

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

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

$$\widehat{\sigma}^{11} = \frac{1}{n\varepsilon_n^2}[2pl(\widehat{\beta}, \widehat{\gamma}) - pl(\widehat{\beta} + \varepsilon_n, \widehat{\gamma}) - pl(\widehat{\beta} - \varepsilon_n, \widehat{\gamma})],$$

$$\widehat{\sigma}^{22} = \frac{1}{n\varepsilon_n^2}[2pl(\widehat{\beta}, \widehat{\gamma}) - pl(\widehat{\beta}, \widehat{\gamma} + \varepsilon_n) - pl(\widehat{\beta}, \widehat{\gamma} - \varepsilon_n)],$$

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

are consistent.

Consistent estimators $\widehat{\sigma}_{ij}$ of the parameters σ_{ij} are obtained take the inverse of the estimated matrix $\widehat{\Sigma}^{-1} = ||\widehat{\sigma}^{ij}||$. The test statistic has the form

$$T = \sqrt{n}\,\frac{\widehat{\gamma}}{\widehat{\sigma}},$$

where

$$\widehat{\sigma} = \widehat{\gamma}^2 \widehat{\sigma}_{11} + 2\widehat{\beta}\widehat{\gamma}\widehat{\sigma}_{12} + \widehat{\beta}^2 \widehat{\sigma}_{22}.$$

The hypothesis H_0 is rejected if $T > z_\alpha$, where z_α is the upper α-quantile of the standard normal distribution.

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