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Non-parametric tests for the two-group comparison with multivariate censored data

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Abstract

We developped a multivariate version of weighted logrank tests to compare two multivariate time-to-event distributions; our method is based on the marginal approach, and uses martingale properties. Our results can be extended to the study of several risk factors in a multivariate proportional hazard model. ***To cite this article: C. Pinçon, C. R. Acad. Sci. Paris, Ser. I 338 (2004).***

Résumé

Tests non-paramétriques de comparaison de deux groupes pour des données censurées multivariées. Nous proposons une nouvelle version multivariée des tests du logrank pondéré pour la comparaison de deux distributions de survie multivariée ; notre méthode s'inscrit dans le cadre de l'approche dite marginale, et utilise les propriétés des martingales. Nos résultats peuvent être généralisés à l'étude de plusieurs facteurs de risque par l'intermédiaire d'une version multivariée des modèles à risques proportionnels. ***Pour citer cet article : C. Pinçon, C. R. Acad. Sci. Paris, Ser. I 338 (2004).***

Version française abrégée

Considérons un échantillon dont les individus sont répartis en deux groupes A et B. Chaque sujet, suivi jusqu'à l'instant τ, peut expérimenter K événements distincts ($K > 1$), susceptibles d'être censurés, mais ne se censurant pas les uns les autres. Nous supposerons par la suite que $K = 2$, mais la généralisation à $K > 2$ critères d'intérêt est immédiate. Le test d'égalité dans les deux groupes des distributions du délai d'apparition d'un seul événement sur $[0, \tau]$ peut s'effectuer en utilisant les tests du logrank pondéré dont on connaît la loi asymptotique sous l'hypothèse nulle (voir par exemple [4,7,3]).

Pour le test d'égalité des distributions conjointes des délais d'apparition de plusieurs événements sur $[0, \tau]$, il est nécessaire de prendre en compte les dépendances entre les différents temps d'événement induites par le fait qu'un même sujet peut expérimenter plusieurs critères d'intérêt. Nous nous sommes intéressés aux méthodes s'inscrivant dans le cadre de l'approche dite marginale [9,10].

Nous proposons une amélioration de ces méthodes en utilisant les propriétés des martingales. Nos résultats sur les covariances des martingales sont similaires à ceux de Prentice et Cai [8] dans le cas non censuré, mais la

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généralisation au cas censuré diffère des extensions qu'ils ont proposées. Nos travaux concernent la distribution de notre statistique de test sous l'hypothèse nulle $H_0 : \{\Lambda_{1A} = \Lambda_{1B}, \Lambda_{2A} = \Lambda_{2B}\}$, ainsi que sous une série d'alternatives locales $H_{1,n}$. Nous proposons également une généralisation de ces tests pour une version multivariée des modèles à risques proportionnels.

1. Preliminaries

Equality of two survival distributions when there is a single, possibly censored, time-to-failure observed for each subject can be tested with weighted logrank statistics, whose asymptotic distribution under the null hypothesis is well known [4,7,3]. However one can be interested in studying more than one type of event for each individual; for example, a randomized comparative trial can be designed to test effects of a new treatment on the time before patients develop several kinds of symptoms. To compare treated patients to the placebo group, we have to use these multivariate data to test whether the joint distributions of the failure times are equal in both groups.

Let groups A and B have size n_A and n_B $(n_A + n_B = n)$. Let (T_{1ji}, T_{2ji}) be the times to failure in group j $(j = A, B)$ for the ith subject $(i = 1, \ldots, n_j)$; the couples $\{(T_{1ji}, T_{2ji}),\ i = 1, \ldots, n_j\}$ are assumed to be i.i.d. with continuous joint survival function $\overline{F}_j(t_1, t_2) = \Pr\{T_{1ji} > t_1, T_{2ji} > t_2\}$. Let (C_{1ji}, C_{2ji}) be the censoring time, so that we only observe (X_{1ji}, X_{2ji}), where $X_{kji} = (T_{kji} \wedge C_{kji})$, and $(\delta_{1ji}, \delta_{2ji})$ where $\delta_{kji} = 1\{T_{kji} < C_{kji}\}$. The couples $\{(C_{1ji}, C_{2ji}),\ i = 1, \ldots, n_j\}$ are assumed to be independent of each couple (T_{1ji}, T_{2ji}) and mutually independent, with joint survival function $\overline{G}(t_1, t_2)$.

For $k = 1, 2,\ j = A, B,\ i = 1, \ldots, n_j$, we introduce the following processes: $Y_{kji}(t) = 1\{X_{kji} \geqslant t\}$, $N_{kji}(t) = 1\{T_{kji} < C_{kji}, T_{kji} \leqslant t\}$, $M_{kji}(t) = N_{kji}(t) - \int_0^t Y_{kji}(s)\,\mathrm{d}\Lambda_{kj}(s)$ where Λ_{kj} is the cumulative hazard function of the kth event in the jth group. Then, $\overline{Y}_{kj} = \sum_{i=1}^{n_j} Y_{kji}$ and $\overline{Y}_k = \overline{Y}_{kA} + \overline{Y}_{kB}$ (idem for $\overline{N}_{kj}$, $\overline{M}_{kj}$, $\overline{N}_k$ and $\overline{M}_k$). We note $r_j(t_1, t_2) = \sum_{i=1}^{n_j} Y_{1ji}(t_1)Y_{2ji}(t_2)$ and $r(t_1, t_2) = r_A(t_1, t_2) + r_B(t_1, t_2)$. The maximum follow-up time is $\tau < \infty$, and such as $\overline{Y}_k(\tau) > 0$. Let $\bar{y}_{kj} = \overline{F}_{kj}\overline{G}_k$ and $\bar{y}_k = \{\rho_A \bar{y}_{kA} + \rho_B \bar{y}_{kB}\}$ be the uniform limits of means $\overline{Y}_{kj}/n_j$ and $\overline{Y}_k/n$ respectively, where $\rho_j = \lim n_j/n$ as $n \to \infty$.

We consider Nelson and Aalen estimates [1,5] of cumulative hazard functions $\hat{\Lambda}_{kj}(t) = \int_0^t \frac{\mathrm{d}\overline{N}_{kj}(s)}{\overline{Y}_{kj}(s)}$ for $j = A, B$ and $\hat{\Lambda}_k(t) = \int_0^t \frac{\mathrm{d}\overline{N}_k(s)}{\overline{Y}_k(s)}$.

The logrank statistic for the kth event is:

$$LR_k = n^{-1/2} \int_0^\tau W_k(s) \frac{\overline{Y}_{kA}\overline{Y}_{kB}}{\overline{Y}_k}(s) \left\{ \frac{\mathrm{d}\overline{N}_{kA}}{\overline{Y}_{kA}} - \frac{\mathrm{d}\overline{N}_{kB}}{\overline{Y}_{kB}} \right\}(s), \tag{1}$$

where $W_k(t)$ is a predictable process that uniformly converges in probability to $w_k(t)$ as $n \to \infty$.

2. Asymptotic distribution under H_0: $\{\Lambda_{1A} = \Lambda_{1B},\ \Lambda_{2A} = \Lambda_{2B}\}$ on $[0; \tau]$

Under H_0, the marginal survival distributions are supposed equal in both groups, say $\Lambda_{1A} = \Lambda_{1B} = \Lambda_1$, $\Lambda_{2A} = \Lambda_{2B} = \Lambda_2$, where Λ_k denotes the unknown cumulative hazard function for $k = 1, 2$.

Theorem 2.1. *Under H_0, vector $(LR_1, LR_2)'$ converges in distribution as $n \to \infty$ to a multivariate normal distribution with null expectation and matrix of variance covariance $\Sigma = (\sigma_{kk'})$ $(k = 1, 2,\ k' = 1, 2)$ where:*

$$\sigma_{kk'} = \int_0^\tau\!\!\int_0^\tau \rho_A \rho_B \frac{w_k(s) w_{k'}(u)}{\bar{y}_k(s)\bar{y}_{k'}(u)} \bigl\{ \rho_B \bar{y}_{kB}(s)\bar{y}_{k'B}(u) v_{kk'A}(\mathrm{d}s, \mathrm{d}u) + \rho_A \bar{y}_{kA}(s)\bar{y}_{k'A}(u) v_{kk'B}(\mathrm{d}s, \mathrm{d}u) \bigr\}, \tag{2}$$

with, for $j = A, B$

$$v_{kk'j}(t_k, t_{k'}) = \int_0^{t_k}\int_0^{t_{k'}} E\{\mathrm{d}M_{kji}(s)\,\mathrm{d}M_{k'ji}(u)\}$$

equal to

$$\int_0^{t_k}\int_0^{t_{k'}} \overline{G}(s,u)\{f(s,u)\,\mathrm{d}s\,\mathrm{d}u + \mathrm{d}\Lambda_k(s)\overline{F}(s,\mathrm{d}u) + \mathrm{d}\Lambda_{k'}(u)\overline{F}(ds,u) + \mathrm{d}\Lambda_k(s)\,\mathrm{d}\Lambda_{k'}(u)\overline{F}(s,u)\},$$

where $\overline{F}(t_1,t_2) = \Pr\{T_{1ji} > t_1, T_{2ji} > t_2\}$ *and* $f(t_1,t_2)$ *is the density function.*

A consistent estimator of $v_{kk'j}(t_k, t_{k'})$ is

$$\hat{v}_{kk'j}(t_k, t_{k'}) = n_j^{-1}\int_0^{t_k}\int_0^{t_{k'}} \sum_{i=1}^{n_j} Y_{kji}(s)Y_{k'ji}(u)\widehat{E}(\mathrm{d}M_{kji}(s)\,\mathrm{d}M_{k'ji}(u)|Y_{kji}(s)Y_{k'ji}(u)=1),$$

where the conditional expectation can be consistently estimated (see, e.g., [2]), by

$$\widehat{E}(\mathrm{d}M_{kji}(s)\,\mathrm{d}M_{k'ji}(u)|Y_{kji}(s)Y_{k'ji}(u)=1) = r^{-1}(s,u)\sum_{j=A}^{B}\sum_{i=1}^{n_j}\mathrm{d}\widehat{M}_{kjl}(s)\,\mathrm{d}\widehat{M}_{k'jl}(u),$$

introducing the martingale residuals $\widehat{M}_{kjl}(t) = N_{kjl}(t) - \int_0^t Y_{kjl}(s)\,\mathrm{d}\hat{\Lambda}_k(s)$.

Consequently:

Proposition 2.2. *Under* H_0, *a consistent estimator of* $v_{kk'j}(t_k, t_{k'})$ *is*

$$\hat{v}_{kk'j}(t_k, t_{k'}) = n_j^{-1}\int_0^{t_k}\int_0^{t_{k'}} \frac{r_j(s,u)}{r(s,u)}\sum_{j=A}^{B}\sum_{l=1}^{n_j}\mathrm{d}\widehat{M}_{1jl}(s)\,\mathrm{d}\widehat{M}_{2jl}(u). \tag{3}$$

On substituting this above formula into (2), we find:

Proposition 2.3. *Under* H_0, *the matrix* $\widehat{\Sigma} = (\hat{\sigma}_{kk'})$ $(k=1,2,\ k'=1,2)$ *with*:

$$\hat{\sigma}_{kk'} = n^{-1}\int_0^{\tau}\int_0^{\tau}\left\{\frac{W_k(s)W_{k'}(u)}{\overline{Y}_k(s)\overline{Y}_{k'}(u)} \times \left[\overline{Y}_{kB}(s)\overline{Y}_{k'B}(u)r_A(s,u) + \overline{Y}_{kA}(s)\overline{Y}_{k'A}(u)r_B(s,u)\right]\frac{\sum_{j=A}^{B}\sum_{i=1}^{n_j}\mathrm{d}\widehat{M}_{kji}(s)\,\mathrm{d}\widehat{M}_{k'ji}(u)}{r(s,u)}\right\}$$

is an unbiased estimate of the matrix Σ.

From this proposition we deduce the following result for testing H_0: $\{\Lambda_{1A} = \Lambda_{1B},\ \Lambda_{2A} = \Lambda_{2B}\}$ on $[0;\tau]$:

Theorem 2.4. *A test statistic to test* H_0 *against an unspecified alternative hypothesis is*:

$$K = (LR_1, LR_2)\widehat{\Sigma}^{-1}(LR_1, LR_2)', \tag{4}$$

which asymptotically follows a chi-square distribution with two degrees of freedom.

3. Asymptotic distribution under a sequence of local alternatives $\mathrm{H}_{1,n}$

In the first part, we derived a multivariate test statistic to test H_0 without specifying any particular kind of alternative hypotheses. We focus now on alternative hypotheses with the following form: $\mathrm{H}_{1,n}$: $\Lambda_{kj}(t) = \int_0^t \{1 + n^{-1/2}\theta_{kj}(s)\}\,\mathrm{d}\Lambda_k(s)$ for $k = 1, 2$ and $j = A, B$, and where functions θ_{kj} are bounded on $[0; \tau]$ [6]. We keep former notations, but expressions depending on cumulative hazard functions Λ_{kA} and Λ_{kB} are different. The weighted logrank statistic family for event k (1) is, under $\mathrm{H}_{1,n}$:

$$LR_k = n^{-1/2}\int_0^\tau W_k(s)\left\{\frac{\overline{Y}_{kB}}{\overline{Y}_k}\,\mathrm{d}\overline{M}_{kA} - \frac{\overline{Y}_{kA}}{\overline{Y}_k}\,\mathrm{d}\overline{M}_{kB}\right\}(s) + n^{-1}\int_0^\tau W_k(s)\frac{\overline{Y}_{kA}\overline{Y}_{kB}}{\overline{Y}_k}(s)\{\theta_{kA} - \theta_{kB}\}(s)\,\mathrm{d}\Lambda_k(s),$$

where, for $j = A, B$, $i = 1, \ldots, n_j$, $M_{kji}(t) = N_{kji}(t) - \int_0^t Y_{kji}(s)\{1 + n_k^{-1/2}\theta_{kj}(s)\}\,\mathrm{d}\Lambda_k(s)$ and $\overline{M}_{kj} = \sum_{i=1}^{n_j} M_{kji}$.

Theorem 3.1. *Under $\mathrm{H}_{1,n}$, vector $(LR_1, LR_2)'$ converges in distribution to a multivariate normal distribution with expectation $(\mu_1, \mu_2)'$, where, for $k = 1, 2$:*

$$\mu_k = \int_0^\tau w_k(s)\rho_A\rho_B\frac{\bar{y}_{kA}\bar{y}_{kB}}{\bar{y}_k}(s)\bigl\{\theta_{kA}(s) - \theta_{kB}(s)\bigr\}\,\mathrm{d}\Lambda_k(s)$$

and with variance covariance matrix $\Sigma = (\sigma_{kk'})$ $(k = 1, 2,\ k' = 1, 2)$, where:

$$\sigma_{kk'} = \int_0^\tau\int_0^\tau \rho_A\rho_B\frac{w_k(s)w_{k'}(u)}{\bar{y}_k(s)\bar{y}_{k'}(u)}\bigl\{\rho_B\,\bar{y}_{kB}(s)\bar{y}_{k'B}(u)v_{kk'A}(\mathrm{d}s, \mathrm{d}u) + \rho_A\,\bar{y}_{kA}(s)\bar{y}_{k'A}(u)v_{kk'B}(\mathrm{d}s, \mathrm{d}u)\bigr\},$$

with, for $j = A, B$

$$v_{kk'j}(t_k, t_{k'}) = \int_0^{t_k}\int_0^{t_{k'}} E\bigl\{\mathrm{d}M_{kji}(s)\,\mathrm{d}M_{k'ji}(u)\bigr\}$$

equal to

$$v_{kk'j}(\mathrm{d}s, \mathrm{d}u) = \overline{G}(s, u)\bigl\{f_j(s, u)\,\mathrm{d}s\,\mathrm{d}u + \mathrm{d}\Lambda_{kj}(s)\overline{F}_j(s, \mathrm{d}u) + \mathrm{d}\Lambda_{k'j}(u)\overline{F}_j(\mathrm{d}s, u) + \mathrm{d}\Lambda_{kj}(s)\,\mathrm{d}\Lambda_{k'j}(u)\overline{F}_j(s, u)\bigr\},$$

where $\overline{F}_j(t_1, t_2) = \Pr\{T_{kji} > t_1, T_{k'ji} > t_2\}$ and $f_j(t_1, t_2)$ is the density function.

As under null hypothesis, a consistent estimator of $v_{kk'j}(t_k, t_{k'})$ is

$$\hat{v}_{kk'j}(t_k, t_{k'}) = n_j^{-1}\int_0^{t_k}\int_0^{t_{k'}}\sum_{i=1}^{n_j} Y_{kji}(s)Y_{k'ji}(u)\widehat{E}\bigl(\mathrm{d}M_{kji}(s)\,\mathrm{d}M_{k'ji}(u)|Y_{kji}(s)Y_{k'ji}(u) = 1\bigr),$$

where the conditional expectation is now consistently estimated by

$$\widehat{E}\bigl(\mathrm{d}M_{kji}(s)\,\mathrm{d}M_{k'ji}(u)|Y_{kji}(s)Y_{k'ji}(u) = 1\bigr) = r_j^{-1}(s, u)\sum_{i=1}^{n_j}\mathrm{d}\widehat{M}_{kjl}(s)\,\mathrm{d}\widehat{M}_{k'jl}(u),$$

with the martingale residuals

$$\widehat{M}_{kjl}(t) = N_{kjl}(t) - \int_0^t Y_{kjl}(s)\,\mathrm{d}\hat{\Lambda}_{kj}(s).$$

Then:

Proposition 3.2. *Under* $\mathrm{H}_{1,n}$, *a consistent estimator of* $\upsilon_{kk'j}(t_k, t_{k'})$ *is*

$$\hat{\upsilon}_{kk'j}(t_k, t_{k'}) = n_j^{-1} \int_0^{t_k} \int_0^{t_{k'}} \sum_{l=1}^{n_j} \mathrm{d}\widehat{M}_{1jl}(s)\, \mathrm{d}\widehat{M}_{2jl}(u).$$

Proposition 3.3. *Under* $\mathrm{H}_{1,n}$, $\widehat{\Sigma} = (\hat{\sigma}_{kk'})$ $(k = 1, 2,\ k' = 1, 2)$:

$$\hat{\sigma}_{kk'} = n^{-1} \int_0^{\tau}\int_0^{\tau} \frac{W_k(s) W_{k'}(u)}{\overline{Y}_k(s)\overline{Y}_{k'}(u)} \times \left\{ \overline{Y}_{kB}(s)\overline{Y}_{k'B}(u) \sum_{i=1}^{n_A} \mathrm{d}\widehat{M}_{kAi}(s)\, \mathrm{d}\widehat{M}_{k'Ai}(u) + \overline{Y}_{kA}(s)\overline{Y}_{k'A}(u) \sum_{i=1}^{n_B} \mathrm{d}\widehat{M}_{kBi}(s)\, \mathrm{d}\widehat{M}_{k'Bi}(u) \right\}$$

is an unbiased estimate of Σ.

Then:

Theorem 3.4. *Under* $\mathrm{H}_{1,n}$, *the test statistic* $K = (LR_1, LR_2)\widehat{\Sigma}^{-1}(LR_1, LR_2)'$ *asymptotically follows a non-central chi-square distribution with two degrees of freedom, whose non-centrality parameter is*:

$$e = (\mu_1, \mu_2)\Sigma^{-1}(\mu_1, \mu_2)'.$$

For the test of H_0 *against* $\mathrm{H}_{1,n}$ *at level* α, *the asymptotic power of* K *statistic is*

$$1 - \Psi_\nu\left(k_\alpha \left[1 + \frac{e}{2+e}\right]^{-1}\right),$$

where, for a central chi-square distribution with two degrees of freedom χ_2^2, $\Pr\{\chi_2^2 < k_\alpha\} = 1 - \alpha$, *and* $\Psi_\nu(x) = \Pr\{\chi_\nu^2 < x\}$, *where* $\nu = (2+e)^2/(2+2e)$.

The power of the test can then be estimated using an estimate of e *computed with the expressions we established.*

4. What if censoring in group A differs from censoring in group B?

We had supposed that the couples of censoring times (C_{1ji}, C_{2ji}) had the same bivariate distribution in both groups, but we can relax this assumption, in letting vectors $(C_{1ji}, C_{2ji})'$ have different distributions in group A and group B. In this case, former expressions have to be modified, to obtain:

Theorem 4.1. *Under* H_0, $(LR_1, LR_2)'$ (*defined by* (1)) *converges in distribution as* $n \to \infty$ *to a multivariate normal distribution, with null expectation and with variance covariance matrix* $\Sigma = (\sigma_{kk'})$ $(k = 1, 2,\ k' = 1, 2)$ *being consistently estimated by* $\widehat{\Sigma} = (\hat{\sigma}_{kk'})$:

$$\hat{\sigma}_{kk'} = n^{-1} \int_0^{\tau}\int_0^{\tau} \frac{W_k(s) W_{k'}(u)}{\overline{Y}_k(s)\overline{Y}_{k'}(u)} \times \left\{ \overline{Y}_{kB}(s)\overline{Y}_{k'B}(u) \sum_{i=1}^{n_A} \mathrm{d}\widehat{M}_{kAi}(s)\, \mathrm{d}\widehat{M}_{k'Ai}(u) + \overline{Y}_{kA}(s)\overline{Y}_{k'A}(u) \sum_{i=1}^{n_B} \mathrm{d}\widehat{M}_{kBi}(s)\, \mathrm{d}\widehat{M}_{k'Bi}(u) \right\},$$

where $\mathrm{d}\widehat{M}_{kji}(s) = \mathrm{d}N_{kji}(s) - Y_{kji}(s)\, \mathrm{d}\hat{\Lambda}_k(s)$.

5. Extension to a multivariate version of the proportional hazard model

We can generalize the results concerning multivariate weighted logrank statistic to account for $p > 1$ covariates, with finite number of values, or defined on an interval. We keep former notations, deleting subscript j. We consider the well-known Cox model to explain for the kth event the link between the hazard function λ_k and the vector z_i of the p covariates of the ith subject, $i = 1, \ldots, n$: $\lambda_k(t; z_i) = Y_{ki}(t)\lambda_{k0}(t)\,\mathrm{e}^{\beta_k' z_i}$, where λ_{k0} is an unspecified baseline hazard function and β_k is the vector of unknown parameters quantifying effect of covariates on the instantanate hazard. The score function for event k under H_0: $\beta_1 = \beta_2 = 0$ on $[0; \tau]$ is $n^{-1/2}U_k(\tau) = n^{-1/2}\sum_{i=1}^n \int_0^\tau \{z_i - E_k(s)\}\,\mathrm{d}M_{ki}(s)$ with $M_{ki}(t) = N_{ki}(t) - \int_0^t Y_{ki}(s)\lambda_{k0}(s)$ and $E_k(t) = (n^{-1}\sum_{i=1}^n Y_{ki}(t)z_i)/(n^{-1}\sum_{i=1}^n Y_{ki}(t))$ converging uniformly in t to $e_k(t)$.

Result (3) about processes M_{ki} is useful to find the asymptotic distribution of vector $(U_1'(\tau), U_2'(\tau))'$ under H_0: $\beta_1 = \beta_2 = 0$ on $[0; \tau]$:

Theorem 5.1. *Under* H_0, $(n^{-1/2}U_1'(\tau), n^{-1/2}U_2'(\tau))'$ *converges to a multivariate normal distribution with null expectation and with variance covariance matrix* $\Sigma = (\sigma_{kk'})$ $(k = 1, 2,\ k' = 1, 2)$ *where* $\sigma_{kk'}$ *is consistently estimated by*:

$$\hat{\sigma}_{kk'} = n^{-1}\sum_{i=1}^n \int_0^\tau\!\!\int_0^\tau \left\{\left[z_i - E_k(s)\right]\left[z_i - E_{k'}(u)\right]' \frac{Y_{ki}(s)Y_{k'i}(u)}{r(s,u)} \sum_{j=1}^n \mathrm{d}\widehat{M}_{kj}(s)\,\mathrm{d}\widehat{M}_{k'j}(u)\right\}$$

with $\mathrm{d}\widehat{M}_{ki}(t) = \mathrm{d}N_{ki}(t) - Y_{ki}(t)\,\mathrm{d}\hat{\Lambda}_k(t)$.

Then:

Theorem 5.2. *A test statistic to test* H_0: $\beta_1 = \beta_2 = 0$ *on* $[0; \tau]$ *is*:

$$K = \left(n^{-1/2}U_1(\tau), n^{-1/2}U_2(\tau)\right)\widehat{\Sigma}^{-1}\left(n^{-1/2}U_1(\tau), n^{-1/2}U_2(\tau)\right)',$$

which asymptotically follows a chi-square distribution with $2p$ *degrees of freedom.*

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