Proportionality test in the Cox model with correlated covariates

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Abstract   The effect of correlation between covariates on the proportionality test results of a specific covariate in the Cox model is well documented problem by several authors. The first solution has been proposed for the Kolmogorov-Smirnov (KS) test, the Cramér-von Mises (CvM) test, and the Anderson-Darling (AD) test. It consists of simulating the null distribution of these test statistics, since this is only known if the covariates are uncorrelated. The results of the simulations carried out by the proponents of this solution have not proved its effectiveness in all studied cases. The second solution is based on the fact that the score function used in the tests mentioned above, and in the construction of the score tests, assumes that all other covariates are proportional, which is not always true. The idea is therefore to introduce temporal parameters to these covariates whose meanings match their proportionalities. Such a change in the score function requires estimation of the new parameters introduced for each tested covariate.
In this article, we propose a simple technique to eliminate such an effect. The technique involves changing the covariate to be tested by the residual of its linear regression against the other covariates in the model. This change retains the same null hypothesis to be tested with a new covariate that is uncorrelated with the others. A simulation comparison of these techniques is considered.

1. Introduction

The Cox model [1] is an essential tool in survival analysis, describing the link between survival time and the covariates in a data set. It expresses the death rate of an individual i in the following form:

$$\lambda_i(t) = \lambda_0(t) \exp\left\{ \beta^T X^{(i)} \right\}, \tag{1}$$

where $\beta = (\beta_1, ..., \beta_m)^T$ is the vector of unknown parameters, $X^{(i)} = (X_1^{(i)}, ..., X_m^{(i)})^T$ is the covariates vector for i-th individual, and $\lambda_0(t)$ is an unknown baseline death rate.

The main hypothesis in this model is that the death rates ratio remains constant over time and depends only on the covariates values. This hypothesis may not be verified in several cases. In this context, several tests have been proposed for validation. They are divided into two classes,

Class of global tests or Cox model validation tests. We cite the work of [1, 5, 6, 7, 8, 11, 13, 14]

Class of partial tests. They are used to test the proportionality hypothesis for each covariate separetely (see [2, 3, 4, 12]).

The main tools used in the construction of the most proportionality tests are the following m score functions:

$$U_j(\beta, t) = \sum_{i=1}^{n} \int_0^t \left(X_j^{(i)} - \frac{\sum_{k=1}^{n} Y_k(u) X_j^{(k)} \exp\left\{\beta^T X^{(k)}\right\}}{\sum_{k=1}^{n} Y_k(u) \exp\left\{\beta^T X^{(k)}\right\}} \right) dN_i(u), \ j = 1, ..., m,$$

where n is the number of individuals, $N_i(t)$ and $Y_i(t)$ are respectively the indicator of death and the indicator of risk at time t of the i-th individual. We denote $I_j(\beta, t)$ the inverse derivative of $U_j(\beta, t)$ for $j = 1, ..., m$. The unknown parameters estimators in the (1) model are obtained by solving the system of equations $U_j(\beta, \infty) = 0, \ j = 1, ..., m$. We denote $\hat{\beta} = (\hat{\beta}_1, ..., \hat{\beta}_m)$ the vector of these estimators.

The tests proposed by [2] to test the proportionality of a specific covariate X_p ($1 \le p \le m$) in the (1) model are the classic tests, namely the Kolmogorov-Smirnov (KS), the Cramér-von Mises (CvM) and the Anderson-Darling (AD):

$$KS = \sqrt{J_p(\hat{\beta})} \sup_t \left| U_p(\hat{\beta}, t) \right|, \quad CV = J_p(\hat{\beta}) \int_0^\infty U_p(\hat{\beta}, t)^2 \, d\hat{q}_p(t),$$

$$AD = J_p(\hat{\beta}) \int_0^\infty \frac{U_p(\hat{\beta}, t)^2}{\hat{q}_p(t)(1 - \hat{q}_p(t))} \, d\hat{q}_p(t). \tag{2}$$

where $J_p(\hat{\beta})$ is the p-th diagonal elements of the Fischer information matrix and $\hat{q}_p(t) = \frac{I_p(\hat{\beta}, t)}{J_p(\hat{\beta})}$.

The asymptotic distributions of the statistics of these tests are well determined in condition that the covariates are independent. In the case of correlated covariates, [2] used the Monte Carlo method to simulate these distributions under the null hypothesis. The simulation results showed that this technique does not perform well if the covariates are strongly correlated (Tables 3 and 4 in [2]).

To test the proportionality of X_p, [3] proposed a score test based on the following alternative:

$$\lambda_i(t) = \lambda_0(t) \exp\left\{ \beta^T X^{(i)} + \theta_p^T \xi_p \left(\hat{F}_0(t)/\hat{F}_0(\tau) \right) X_p^{(i)} \right\}, \tag{3}$$

where τ is the maximum time of the experiment, $\xi_p = (\varphi_1, ..., \varphi_{d_p})^T$, φ_k for $k = 1, ..., d_p$ are a smooth functions, bounded in $L_2[0, 1]$ and linearly independent, $\theta_p = (\theta_1^{(p)}, ..., \theta_{d_p}^{(p)})$ is a parameters vector, and $\hat{F}_0 = 1 - \exp\{-\hat{\Lambda}_0\}$ with $\hat{\Lambda}_0$ is the Breslow estimator of the baseline death rate under (1).

[3] also noted that this test score misjudges the proportionality of a proportional covariate if it is highly correlated with another non-proportional one. [4] returns this fact to the formulation of the score test and the classic tests above, which assumes that all the other covariates not concerned by the test are proportional, which is not always the case. To remedy a such behaviour, he introduced a time parameters to these covariates in (3). Their introduction serves to express the actual state of proportionality of each covariate other than the one being tested. The new alternative is written as follows:

$$\lambda_i(t) = \lambda_0(t) \exp\left\{ \beta^T X^{(i)} + \sum_{j=1}^{m} \theta_j^T \xi_j \left(\hat{F}_0(t)/\hat{F}_0(\tau) \right) X_j^{(i)} \right\}, \tag{4}$$

where $\theta_j = (\theta_1^{(j)}, ..., \theta_{d_j}^{(j)})^T$ and $\xi_j = (\varphi_1, ..., \varphi_{d_j})^T$ for $j = 1, ..., m$.

The null hypothesis to be tested becomes

$$H_0 : \theta_p = (0, ..., 0). \tag{5}$$

Under H_0, the vector of the corresponding $(m+d)$-score functions (with $d = \sum\limits_{j=1}^{m} d_j$) is written:

$$
\left\{
\begin{array}{l}
U_{j0}(\beta,\theta,t) = \sum\limits_{i=1}^{n} \int_0^t \left(X_j^{(i)} - \dfrac{\sum\limits_{k=1}^{n} Y_k(u) X_j^{(k)} \exp\left\{ \beta^T X^{(k)} + \sum\limits_{\substack{j=1 \\ j\neq p}}^{m} \theta_j^T \psi_j(t) X_j^{(k)} \right\}}{\sum\limits_{k=1}^{n} Y_k(u) \exp\left\{ \beta^T X^{(k)} + \sum\limits_{\substack{j=1 \\ j\neq p}}^{m} \theta_j^T \psi_j(t) X_j^{(k)} \right\}} \right) dN_i(u) \\[3em]
U_{jl}(\beta,\theta,t) = \sum\limits_{i=1}^{n} \int_0^t \psi_l(t) \left(X_j^{(i)} - \dfrac{\sum\limits_{k=1}^{n} Y_k(u) X_j^{(k)} \exp\left\{ \beta^T X^{(k)} + \sum\limits_{\substack{j=1 \\ j\neq p}}^{m} \theta_j^T \psi_j(t) X_j^{(k)} \right\}}{\sum\limits_{k=1}^{n} Y_k(u) \exp\left\{ \beta^T X^{(k)} + \sum\limits_{\substack{j=1 \\ j\neq p}}^{m} \theta_j^T \psi_j(t) X_j^{(k)} \right\}} \right) dN_i(u)
\end{array}
\right. , \tag{6}
$$

with $\psi_j(t) = \xi_j\left(\hat{F}_0(t)/\hat{F}_0(\tau) \right)$ for $l = 1, ..., d_j$ and $j = 1, ..., m$.

The resolution of the sub-system extracted from (6)

$$
\left\{
\begin{array}{l}
U_{j0}(\beta,\theta,\tau) = 0, \\
U_{jl}(\beta,\theta,\tau) = 0, \text{ for } j \neq p \text{ and } l = 1, ..., d_j
\end{array}
\right. , \text{ for } j = 1, ..., m
$$

allows the parameters estimation of the model (4) under H_0. We denote $\hat{\beta}^*$ and $\hat{\theta}$ the vectors of the obtained estimators. Note that their estimation is necessary for each proportionality test of each covariate. On the other hand the remaining sub-system from (6) with replacing the vectors β and θ by their estimators $\hat{\beta}^*$ and $\hat{\theta}$ respectively:

$$
U_{pl}(\hat{\beta}^*, \hat{\theta}, \tau), \text{ for } l = 1, ..., d_p
$$

presents the essential part in the test statistic of H_0. The test, which we denote (*Kr.score*), is a chi-square with d_p degrees of freedom. The classical tests (2) adapted to the alternative (4), are denoted (*Kr.KS*), (*Kr.CV*) et (*Kr.AD*).

In this article, we propose a reformulation of the score tests, in particular that of [3], using a simple technique that eliminate the effect of correlation between the covariates on the test result. This technique consists of replacing the covariate under the test by its residual from its linear regression as a function of the other covariates. It will also be applied to the classic tests mentioned above. The structure of the paper will be as follows: in section 2, we present this proposed reformulation in detail. In Section 3, a simulation study will be carried out to examine the results of this test reformulation application in the presence of correlation between covariates and to compare them with those of the [4] test. We finish with a conclusion

2. Proposed reformulation

The score tests which are the subject of the proposed reformulation are based on the following general alternative:

$$
\lambda_i(t) = \lambda_0(t) \exp\left\{ \beta^T X^{(i)} + \Psi(t, \theta_p) X_p^{(i)} \right\}, i \in \{1, ..., n\} \tag{7}
$$

such that Ψ is a real function which verifies $\Psi(t, 0) = 0$ and $\theta_p = (\theta_p^{(1)}, ..., \theta_p^{(d_p)})$. It is clear that the alternative (3) is part of the class (7).
As mentioned at the beginning of this article, the presence of the correlation between the covariate X_p and the others, especially if one of them is non-proportional, falsifies the results of the score tests. To remedy this problem, and before proceeding with the test score construction, we propose a change in the covariates space. We express the covariate X_p as a function of the other covariates using the following linear model:

$$
X_p = \sum_{\substack{j=1 \\ j\neq p}}^{m} a_j X_j + Z_p,
$$

where Z_p is the residual of this adjustment. With this change, the alternative (7) becomes

$$\lambda_i(t) = \lambda_0(t) \exp\left\{\tilde{\beta}^T \tilde{X}^{(i)} + \Psi(t, \theta_p)\tilde{X}_p^{(i)}\right\}, \, i \in \{1, ..., n\}, \tag{8}$$

such that $\tilde{X}^{(i)} = (\tilde{X}_1^{(i)}, ..., \tilde{X}_m^{(i)})$ and $\tilde{\beta} = (\tilde{\beta}_1, ..., \tilde{\beta}_m)$ are, respectively, the new covariate vector of the i-th individual and the vector of new parameters with

$$\begin{cases} \tilde{X}_j^{(i)} = X_j^{(i)} \text{ and } \tilde{\beta}_j = \beta_j + \beta_p a_j, \text{ if } j \neq p \\ \tilde{X}_p^{(i)} = X_p^{(i)} \text{ and } \tilde{\beta}_p = \beta_p. \end{cases}$$

We note that X_p and $\tilde{X}_p$ have the same parameter β_p. So testing the propotionality of X_p is equivalent to checking that of $\tilde{X}_p$ which is uncorrelated with $\tilde{X}_j, j = 1, ..., m$ and $j \neq p$. The proportionality of the covariate $\tilde{X}_p$, according to the alternative (8), is equivalent to the hypothesis H_0 in (5).

Now we turn to the test score construction. The partial likelihood function, according to [9], under the alternative (8) is written as follows

$$L(\tilde{\beta}, \theta_p) = \prod_{i=1}^{n} \left(\int_0^{\infty} \frac{g\left(\tilde{X}^{(i)}, \tilde{X}_p^{(i)}, \tilde{\beta}, \theta_p, u\right)}{\sum\limits_{j=1}^{n} Y_j(u) g\left(\tilde{X}^{(j)}, \tilde{X}_p^{(j)}, \tilde{\beta}, \theta_p, u\right)} dN_i(u) \right)^{\delta_i} \tag{9}$$

such that $g(X, Z, \beta, \theta, t) = \exp\left\{\beta^T X + \Psi(t, \theta)Z\right\}$ and $\delta_i = 1$ if the i-th individual is deceased (0 otherwise).

Then the k-components of the score function obtained by deriving (9) are

$$\begin{aligned} U_{\theta_p}(\tilde{\beta}, \theta_p) &= \frac{\partial}{\partial \theta_p} \log(L(\tilde{\beta}, \theta_p)) \\ &= \sum_{i=1}^{n} \int_0^{\infty} \left(\frac{\partial}{\partial \theta_p} \log\left(g(\tilde{X}^{(i)}, \tilde{X}_p^{(i)}, \tilde{\beta}, \theta_p, u)\right) - \frac{\sum\limits_{j=1}^{n} Y_j(u)\frac{\partial}{\partial \theta_p} g(\tilde{X}^{(j)}, \tilde{X}_p^{(j)}, \tilde{\beta}, \theta_p, u)}{\sum\limits_{j=1}^{n} Y_j(u) g(\tilde{X}^{(j)}, \tilde{X}_p^{(j)}, \tilde{\beta}, \theta_p, u)} \right) dN_i(u). \end{aligned}$$

Under the hypothesis H_0, these functions depend on the parameters vector $\tilde{\beta} = (\tilde{\beta}_1, ..., \tilde{\beta}_m)$ which is unknown. We will therefore replace it by its estimator $\hat{\tilde{\beta}} = (\hat{\tilde{\beta}}_1, ..., \hat{\tilde{\beta}}_m)$ calculated according to the expression

$$\hat{\tilde{\beta}}_j = \begin{cases} \hat{\beta}_j + \hat{\beta}_p a_j, \text{ if } j \neq p \\ \hat{\beta}_p, \text{ if } j = p \end{cases}, \, j = 1, ..., m.$$

Then the test statistic will be

$$\begin{aligned} \hat{U}_j &= U_{\theta_p}(\hat{\tilde{\beta}}, (0, ..., 0)) \\ &= \sum_{i=1}^{n} \int_0^{\infty} \left(\hat{w}^{(i)}(u) - \tilde{E}(u, \hat{\tilde{\beta}}) \right) dN_i(u), \end{aligned}$$

where

$$\hat{w}^{(i)}(u) = \frac{\partial \Psi(u, 0)}{\partial \theta_p} \tilde{X}_p^{(i)}, \quad \tilde{E}(t, \beta) = \frac{\tilde{S}^{(1)}(t, \beta)}{S^{(0)}(t, \beta)},$$

$$S^{(0)}(t, \beta) = \sum_{i=1}^{n} Y_i(t) \exp\left\{\beta^T \tilde{X}^{(i)}\right\}, \quad \tilde{S}^{(1)}(t, \beta) = \sum_{i=1}^{n} Y_i(t) \hat{w}^{(i)}(t) \exp\left\{\beta^T \tilde{X}^{(i)}\right\}.$$

To complete the construction of this test, we need to look for the asymptotic distribution of $\hat{U}_j$ under H_0. We pose

$$E(t, \beta) = \frac{S^{(1)}(t, \beta)}{S^{(0)}(t, \beta)}, \quad S^{(1)}(t, \beta) = \sum_{i=1}^{n} \tilde{X}^{(i)} Y_i(t) \exp\left\{ \beta^T \tilde{X}^{(i)} \right\},$$

$$S^{(2)}(t, \beta) = \sum_{i=1}^{n} \tilde{X}^{(i) \otimes 2} Y_i(t) \exp\left\{ \beta^T \tilde{X}^{(i)} \right\},$$

$$\tilde{S}^{(2)}(t, \beta) = \sum_{i=1}^{n} \hat{w}^{(i)}(t) \tilde{X}^{(i)T} Y_i(t) \exp\left\{ \beta^T \tilde{X}^{(i)} \right\},$$

$$\tilde{\tilde{S}}^{(2)}(t, \beta) = \sum_{i=1}^{n} \widehat{(w^{(i)}(t))}^{\otimes 2} Y_i(t) \exp\left\{ \beta^T \tilde{X}^{(i)} \right\},$$

such that the notation $A^{\otimes 2}$ means AA^T. We denote by $\tilde{\beta}_0$ the true value of $\tilde{\beta}$. The Taylor expansion around $\tilde{\beta}_0$ allows us to write:

$$n^{1/2}(\hat{\tilde{\beta}} - \tilde{\beta}_0) = \left(\Sigma(\tilde{\beta}_0)\right)^{-1} \sum_{i=1}^{n} \int_0^\tau \{\tilde{X}^{(i)} - E(u, \tilde{\beta}_0)\} dM_i(u) + o_p(1),$$

where $\Sigma(\tilde{\beta}_0)$ is the Fisher information matrix under H_0.
Under usual regularity conditions, the Doob-Meier decomposition, and the delta method, we can write

$$n^{-1/2}\hat{U}_j = n^{-1/2} \sum_{i=1}^{n} \int_0^\infty \{\hat{w}^{(i)}(u) - \tilde{E}(u, \hat{\tilde{\beta}})\} dN_i(u) =$$

$$n^{-1/2} \sum_{i=1}^{n} \int_0^\infty \{\hat{w}^{(i)}(u) - \tilde{E}(u, \hat{\tilde{\beta}})\} dM_i(u) +$$

$$n^{-1/2} \int_0^\infty \{\tilde{E}(u, \tilde{\beta}_0) - \tilde{E}(u, \hat{\tilde{\beta}})\} S^{(0)}(u, \tilde{\beta}_0) d\Lambda_0(u).$$

The Taylor expansion applied to the function $\tilde{\beta} \longrightarrow \tilde{E}(u, \tilde{\beta})$ leads to

$$\tilde{E}(u, \hat{\tilde{\beta}}) - \tilde{E}(u, \tilde{\beta}_0) = \frac{\partial \tilde{E}(u, \tilde{\beta}_0)}{\partial \tilde{\beta}} \left(\hat{\tilde{\beta}} - \tilde{\beta}_0 \right).$$

Therefore

$$n^{-1/2}\hat{U}_j = n^{-1/2} \sum_{i=1}^{n} \int_0^\infty \{\hat{w}^{(i)}(u) - \tilde{E}(u, \tilde{\beta}_0)\} dM_i(u) -$$

$$n^{-1} \int_0^\infty \frac{\partial \tilde{E}(u, \tilde{\beta}_0)}{\partial \tilde{\beta}} S^{(0)}(u, \tilde{\beta}_0) d\Lambda_0(u)\, n^{1/2}(\hat{\tilde{\beta}} - \tilde{\beta}_0) + o_p(1) =$$

$$n^{-1/2} \sum_{i=1}^{n} \int_0^\infty \{\hat{w}^{(i)}(u) - \tilde{E}(u, \tilde{\beta}_0)\} dM_i(u) -$$

$$\Sigma_1 \Sigma^{-1} n^{-1/2} \sum_{i=1}^{n} \int_0^\infty \{X^{(i)} - E(u, \tilde{\beta}_0)\} dM_i(u) + o_p(1),$$

where Σ and Σ_1 are respectively the probability limits of the random matrices,

$$\hat{\Sigma} = n^{-1} \int_0^\infty V(u, \hat{\tilde{\beta}}) dN(u), \quad \hat{\Sigma}_1 = n^{-1} \int_0^\infty \tilde{V}(u, \hat{\tilde{\beta}}) dN(u),$$

$$V(t, \tilde{\beta}) = \frac{S^{(2)}(t, \tilde{\beta})}{S^{(0)}(t, \tilde{\beta})} - \left(E(t, \tilde{\beta}) \right)^{\otimes 2}, \quad \tilde{V}(t, \tilde{\beta}) = \frac{\tilde{S}^{(2)}(t, \tilde{\beta})}{S^{(0)}(t, \tilde{\beta})} - \tilde{E}(t, \tilde{\beta}) E^T(t, \tilde{\beta}).$$

This implies

$$< n^{-1/2} \hat{U}_j >= n^{-1} \sum_{i=1}^n \int_0^\infty \{\hat{w}^{(i)}(u) - \tilde{E}(u, \tilde{\beta}_0)\}^{\otimes 2} \exp\left\{\beta_0^T \tilde{X}^{(i)}\right\} Y_i(u) d\Lambda_0(u) -$$

$$2\Sigma_1 \Sigma^{-1} n^{-1} \sum_{i=1}^n \int_0^\infty \{\hat{w}^{(i)}(u) - \tilde{E}(u, \tilde{\beta}_0)\} \{X^{(i)} - E(u, \tilde{\beta}_0)\}^T \exp\left\{\beta_0^T \tilde{X}^{(i)}\right\} \times$$

$$Y_i(u) d\Lambda_0(u) + \Sigma_1 \Sigma^{-1} n^{-1} \sum_{i=1}^n \int_0^\infty \{X^{(i)} - E(u, \beta_0)\}^{\otimes 2} \exp\left\{\beta_0^T \tilde{X}^{(i)}\right\} \times$$

$$Y_i(u) d\Lambda_0(u) \Sigma^{-1} (\Sigma_1)^T + o_p(1) = \Sigma_2 - \Sigma_1 \Sigma^{-1} (\Sigma_1)^T + o_p(1),$$

where Σ_2 is the probability limit of

$$\hat{\Sigma}_2 = n^{-1} \int_0^\infty \tilde{\tilde{V}}(u, \hat{\tilde{\beta}}) dN(u),$$

with

$$\tilde{\tilde{V}}(u, \beta) = \frac{\tilde{\tilde{S}}^{(2)}(t, \beta)}{S^{(0)}(t, \beta)} - \left(\tilde{E}(t, \beta) \right)^{\otimes 2}.$$

Similarly, the Lindeberg condition (see [9])

$$n^{-1} \sum_{i=1}^n \int_0^\infty \{\hat{w}_j^{(i)}(u) - \tilde{E}_j(u, \beta_0)\}^2 \mathbf{1}_{\{|\hat{w}_j^{(i)}(u) - \tilde{E}_j(u, \beta_0)| \geq \sqrt{n}\varepsilon\}} e^{\beta_0^T X^{(i)}} Y_i(u) d\Lambda_0(u) \xrightarrow{P} 0.$$

is satisfied. This implies that the stochastic process $n^{-1/2} \hat{U}_j$ converges to the Gaussian distribution with mean 0. In particular,

$$n^{-1/2} \hat{U}_j \xrightarrow{D} N(0, W),$$

where $W = \Sigma_2 - \Sigma_1 \Sigma^{-1} (\Sigma_1)^T$.

Finally, to test the null hypothesis H_0, the score test statistic, which we denote (*Re.score*), is

$$T_{sc} = \hat{U}_j^2 / \hat{W},$$

where $\hat{W} = n \left(\hat{\Sigma}_2 - \hat{\Sigma}_1 \hat{\Sigma}^{-1} (\hat{\Sigma}_1)^T \right)$. T_{sc} is asymptotically $\chi_{d_p}^2$ distributed when n tends towards ∞. Consequently, H_0 is rejected with a significance level α if $T_{sc} > \chi_{1-\alpha}^2(d_p)$ where $\chi_{1-\alpha}^2(d_p)$ is the $(1 - \alpha)$ critical value of the $\chi_{d_p}^2$ distribution.

By replacing $\hat{\beta}$ and X, respectively by $\hat{\tilde{\beta}}$ and $\tilde{X}$, in (2), we obtain the classical tests statistics under the proposed reformulation. We denote them by (*Re.KS*), (*Re.CV*) and (*Re.AD*).

3. Simulation study

In this section, we conduct a simulation study to examine the performance of the proposed reformulation. We compare the results obtained with those of the application of the technique proposed by [4]. Thus the function Ψ in (8) must take the following form:

$$\Psi(t, \theta_p) = \theta_p^T \xi_p \left(\hat{F}_0(t)/\hat{F}_0(\tau) \right)$$

for the alternative used for this comparison to be the same.

3.1. Simulation setting

In this study, we consider two cases to examine the power and significance level of the tests presented in the previous sections. In the first case, the ratio of death rates is monotonic as a function of time, while in the second, it is non-monotonic.

The number of repetitions is 5000. For the number of individuals, two values are considered: $n = 100, 200$. We denote by $X = (X_1, X_2)$ the pair of covariates generated from the multinormal distribution with mean (4.4) and variance-covariance matrix

$$\begin{pmatrix} 1 & \rho \\ \rho & 1 \end{pmatrix}$$

such that ρ is the correlation between X_1 and X_2. For ρ, we took the following values: 0.3, 0.5, 0.7, 0.8, and 0.9. The simulations were carried out using the R language [15]. Now, we present the two cases used to generate the data.

3.1.1. Case 1: In this first case, we consider the following model :

$$\lambda_x(t) = \exp\{0.6tX_1 - 0.5X_2\}. \tag{10}$$

The ratio of death rates under (10), is clearly monotonic as a function of time.
To generate the times of death from (10), we use the following expression

$$T_i = \log\left(1 - 0.6X_1 \exp\{0.5X_2\} \log(U_i)\right), \text{ for } i = 1, ..., n,$$

where U_i is the i-th element of a n-values sequence generated from the Uniform[0,1].
The censoring times are generated from the Exponential distribution with parameter 0.28, which gives an average percentage of censoring over the 5000 repetitions equal to 19.82%.

3.1.2. Case 2: To generate the death times, in this case we use the following model:

$$\lambda_X(t) = \exp\{(0.2 + 0.75 \times \mathbf{1}_{[0.7,1]}(t))X_1 - 0.5X_2\}. \tag{11}$$

This is done using the expression

$$T_i = \begin{cases} -\log(U_i)/A_1, & \text{si } U_i > A_3 \\ -\log(U_i)/A_1 + 0.7A_2, & \text{si } A_3 \leq u \leq A_4 \\ -\log(U_i)/A_1 + 0.3A_2, & \text{si } u < A_4 \end{cases} \text{, for } i = 1, ..., n$$

with U_i, $i = 1, ..., n$, is a sequence of values generated according to the Uniform[0,1] and

$$\begin{cases} A_1 = \exp\{0.2X_1 - 0.5X_2\} \\ A_2 = 1 - \exp\{-0.75X_1\} \\ A_3 = \exp\{-0.7A_1\} \\ A_4 = \exp\{-A_1(0.7 + 0.3\exp\{0.75X_1\})\} \end{cases}.$$

We note that the ratio of death rates under the (11) model is non-monotonic as a function of time. The censoring times are generated from the Exponential distribution with parameter 0.53. The average censoring percentage over the 5000 repetitions is equal to 38.47%. censoring probability p and different sample sizes n

3.2. Simulation results

n	ρ	covar.	Kr.Score	Kr.KS	Kr.CV	Kr.AD	Re.Score	Re.KS	Re.CV	Re.AD
100	0.3	X_1	0.2658	0.2748	0.3686	0.3808	0.2630	0.2852	0.4082	0.4186
		X_2	0.0578	0.0428	0.0536	0.0586	0.0540	0.0384	0.0534	0.0570
	0.5	X_1	0.2290	0.2664	0.3204	0.3388	0.2322	0.2380	0.3486	0.3606
		X_2	0.0592	0.0542	0.0568	0.0674	0.0586	0.0358	0.0516	0.0564
	0.7	X_1	0.1682	0.2790	0.2668	0.3086	0.1730	0.1742	0.2558	0.2642
		X_2	0.0508	0.0890	0.0606	0.0926	0.0474	0.0320	0.0464	0.0458
	0.8	X_1	0.1308	0.3038	0.2260	0.3050	0.1288	0.1218	0.1836	0.1916
		X_2	0.0604	0.1600	0.0852	0.1494	0.0552	0.0362	0.0512	0.0542
	0.9	X_1	0.0960	0.4846	0.2734	0.4544	0.0930	0.0822	0.1278	0.1318
		X_2	0.0604	0.3944	0.1712	0.3628	0.0570	0.0324	0.0508	0.0518
200	0.3	X_1	0.5060	0.5506	0.6594	0.6736	0.5372	0.5742	0.6986	0.7142
		X_2	0.0544	0.0406	0.0478	0.0466	0.0600	0.0424	0.0554	0.0560
	0.5	X_1	0.4424	0.5302	0.5910	0.6096	0.4692	0.5116	0.6294	0.6434
		X_2	0.0664	0.0650	0.0584	0.0650	0.0624	0.0422	0.0554	0.0580
	0.7	X_1	0.3076	0.4746	0.4612	0.4980	0.3166	0.3450	0.4550	0.4654
		X_2	0.0510	0.0958	0.0620	0.0708	0.0600	0.0364	0.0504	0.0506
	0.8	X_1	0.2156	0.4728	0.3828	0.4416	0.2228	0.2484	0.3386	0.3462
		X_2	0.0518	0.1678	0.0736	0.1138	0.0490	0.0332	0.0428	0.0464
	0.9	X_1	0.1448	0.6110	0.3480	0.5122	0.1348	0.1394	0.1918	0.1940
		X_2	0.0552	0.4136	0.1462	0.2978	0.0554	0.0388	0.0478	0.0528

Table 1. Estimated rejection probabilities of the proportionality hypothesis of X_1 and X_2 for different values of n and ρ in case 1
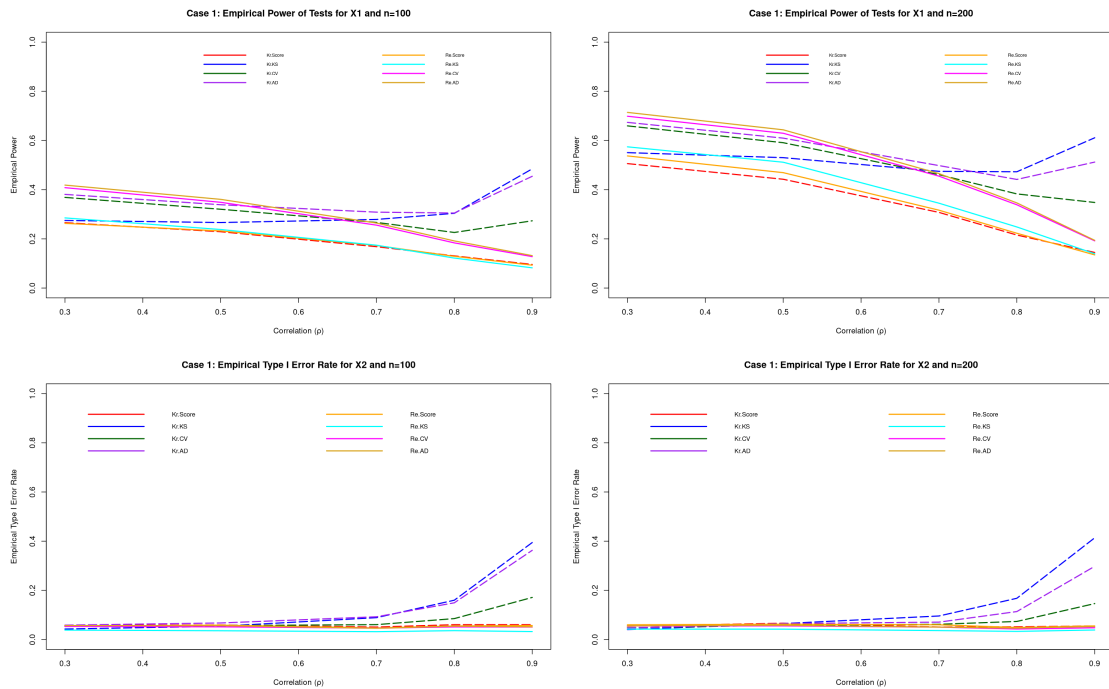

Figure 1. Empirical Power and Type I Error Rate Curves across ρ in case 1

n	ρ	covar.	*Kr.Score*	*Kr.KS*	*Kr.CV*	*Kr.AD*	*Re.Score*	*Re.KS*	*Re.CV*	*Re.AD*
100	0.3	X_1	0.4176	0.4592	0.4888	0.4834	0.4076	0.4346	0.4994	0.4802
		X_2	0.0736	0.0458	0.0556	0.0620	0.0514	0.0376	0.0564	0.0580
	0.5	X_1	0.3540	0.4382	0.4380	0.4462	0.3472	0.3564	0.4228	0.4070
		X_2	0.0722	0.0620	0.0622	0.0702	0.0498	0.0330	0.0572	0.0558
	0.7	X_1	0.2646	0.4184	0.3626	0.3856	0.2410	0.2376	0.2926	0.2822
		X_2	0.0684	0.1034	0.0702	0.0986	0.0532	0.0330	0.0494	0.0502
	0.8	X_1	0.2084	0.4474	0.3480	0.3958	0.1788	0.1738	0.2228	0.2148
		X_2	0.0646	0.1896	0.1076	0.1534	0.0532	0.0378	0.0556	0.0608
	0.9	X_1	0.1418	0.5924	0.3996	0.5162	0.1104	0.0890	0.1278	0.1252
		X_2	0.0658	0.4400	0.2376	0.3714	0.0544	0.0350	0.0540	0.0542
200	0.3	X_1	0.6910	0.7712	0.7546	0.7540	0.7084	0.7524	0.7652	0.7604
		X_2	0.0532	0.0440	0.0510	0.0520	0.0620	0.0388	0.0494	0.0502
	0.5	X_1	0.6206	0.7484	0.7018	0.7132	0.6270	0.6616	0.6870	0.6794
		X_2	0.0638	0.0756	0.0594	0.0628	0.0582	0.0416	0.0514	0.0508
	0.7	X_1	0.4560	0.6842	0.5844	0.6066	0.4400	0.4572	0.4970	0.4866
		X_2	0.0546	0.1348	0.0756	0.0922	0.0508	0.0402	0.0508	0.0508
	0.8	X_1	0.3508	0.6818	0.5194	0.5732	0.3184	0.3248	0.3612	0.3590
		X_2	0.0602	0.2384	0.1064	0.1532	0.0546	0.0382	0.0542	0.0576
	0.9	X_1	0.2168	0.7608	0.5226	0.6408	0.1876	0.1710	0.2068	0.2064
		X_2	0.0568	0.5408	0.2564	0.4118	0.0552	0.0372	0.0488	0.0504

Table 2. Estimated rejection probabilities of the proportionality hypothesis of X_1 and X_2 for different values of n and ρ in case 2
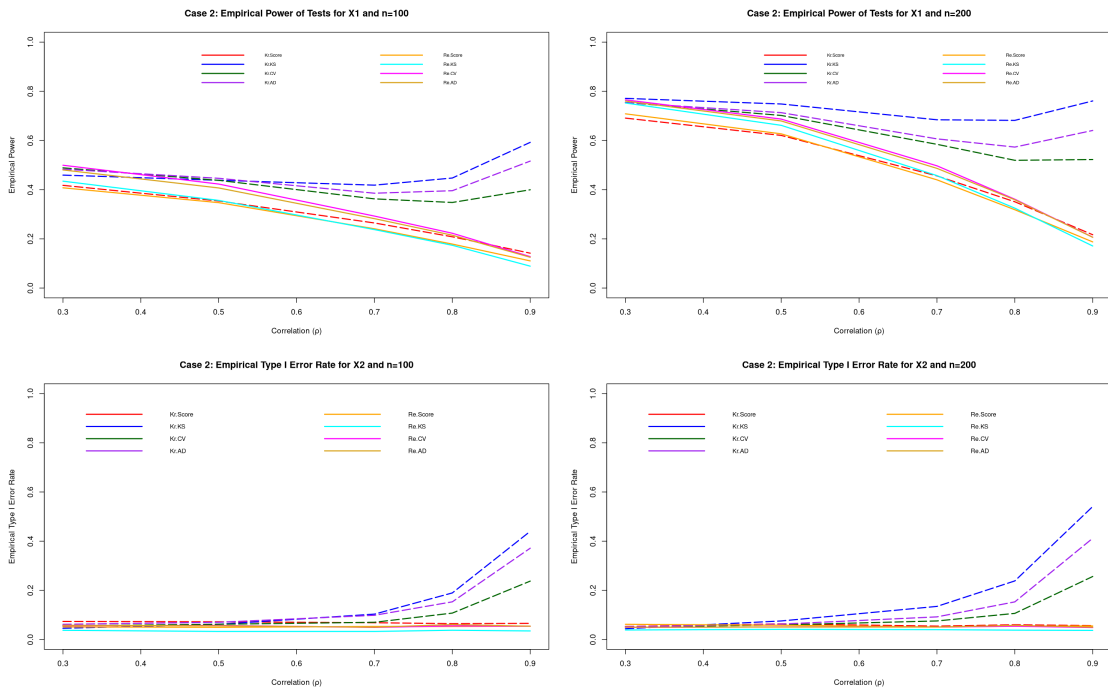

Figure 2. Empirical Power and Type I Error Rate Curves across ρ in case 2

The results of Table 1 and Table 2 show clearly, by testing the proportionality of X_1 and X_2, that the proposed reformulation works well for the different values of n and ρ in the case of the score test and the classical tests. We also note that the technique of [4] led to results similar to those of the proposed reformulation in the case of the score test. For the classical tests, it has difficulty detecting the proportionality of X_2 for large values of ρ.

4. Conclusion

To test the proportionality hypothesis of a specific covariate in the Cox model, a major risk arises when the covariate tested and another non-proportional covariate are correlated. To remedy this problem, a reformulation of the score tests and the classical tests is proposed. The idea is to change the covariate to be tested by a new covariate, which is uncorrelated with the others and has the same proportionality property as the changed covariate. It stands out for its simplicity of implementation and speed of execution compared with the [4] technique, which requires parameter estimation for each proportionality test for each covariate.

A simulation study is carried out to examine and compare the performance of the two techniques. The results clearly show that the proposed reformulation is an effective solution for testing the proportionality of a covariate correlated with the others in the Cox model.

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