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A new approach to estimate correlation coefficients in the presence of censoring and proportional hazards

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Abstract

Estimation of correlations when one of the variables is censored has received only little attention in the past. This presentation reviews the deficiencies of existing approaches and presents an algorithm for the reconstruction of Spearman, Kendall and other nonparametric correlation coefficients from censored samples. The algorithm uses Rubin's technique of multiple imputation and assumes proportionality of hazards as does Cox's model analyses by which it is supposed to supplement. The unbiasedness of the estimation procedure under proportional hazards is demonstrated even for underlying correlations of 0.9 and 90% censoring. Two important applications of the presented procedure are exemplified: The estimation of the correlation of survival time with a prognostic factor and the estimation of the variation of survival explained by prognostic factors within Cox's model.

Keywords: Cox's model; Explained variation; Kendall's tau; Multiple imputation; Spearman's r_s

1. Introduction

Currently, most analyses of survival data are based on the proportional hazards regression model by Cox (1972). Regression coefficients of this model are asymptotically unbiased with noninformative censoring and proportional hazards given. The estimation of related correlation coefficients has received very little

attention and is the topic of this paper. If censoring of survival time is seen as a property of a sample rather than of a population the correlation in an underlying uncensored population should be estimated from censored samples.

All currently available generalizations of nonparametric measures of correlation for censored data including those by Brown et al. (1974) and Harrell (1982) can heavily be biased. Also the parametric and linear Pearson correlation cannot suitably supplement analyses by the semiparametric Cox regression, even if all lifetimes were uncensored.

Also the approaches by Schemper (1990) and Korn and Simon (1990) are not suitable for the assumed uncensored populations of this paper, as the authors themselves describe the dependency of their measures' expectations on the proportion of censoring in samples. As explored recently (Schemper and Stare, 1996) also Nagelkerke's (1991) adjusted R^2 suffers from the same drawback. A measure of squared correlation by Kent and O'Quigley (1988), ρ_w^2 , is unaffected by censoring but is rather complicated and does not have the good interpretability correlation coefficients usually have.

In this paper, we therefore describe a new approach which permits to reconstruct the correlation of an underlying uncensored population in an intuitive way and does not require further assumptions than assumed by a Cox analysis which it will usually supplement.

2. Definition of the procedure

Assume that variables X and T , a lifetime subject to censoring, follow a continuous bivariate distribution, and that we are interested in a measure of correlation of T and X , $\Gamma(T, X)$. We deal with applications, usually medical, where the distribution of T and also the often nonlinear relationship between T and X make parametric correlation $r(T, X)$ or $r(\log T, X)$ unsuitable. We therefore consider Spearman's correlation, $r_s(T, X)$, Kendall's $\tau(T, X)$ and a coefficient $r_{pr}(T, X)$, where 'pr' stands for 'partial ranking'. While $r_s(T, X)$ equals $r(T, X)$ calculated on the ranks of both T and X , r_{pr} is the Pearson correlation r of X and the ranks of T . This is consistent with the semiparametric character of Cox's model which is invariant to monotonic transformations of T but not of X .

As we cannot directly apply these coefficients to possibly censored T we suggest to augment censored survival times with random residual life times to make all survival times uncensored. For this purpose we use Rubin's (1987, 1991) technique of multiple imputation, enforcing consistencies with the estimates from Cox's model (for baseline survival and regression parameters) and with observed conditional distributions of survival times. Several (e.g. 10) such "augmented" data sets are generated, one of the measures of association between the observed t (uncensored or completed) and x being calculated for each and the average, e.g. \bar{r}_{pr} , taken as the result.

Now the algorithm follows in detail:

1. We observe a sample (t_i, x_i) , $i = 1, \dots, n$, and estimate parameters β and baseline survival function $S_0(t)$ for Cox's model with covariate x (preferably standardized to $\bar{x} = 0$).

Note that $\hat{S}_0(t)$ is only defined for $t \leq t^*$ (t^* denoting the maximum observed uncensored life time).

2. Therefore calculate an expected $\hat{S}_0(t)$ for $t > t^*$, $\hat{S}_0^e(t)$, fitting a line to the points $(t^*, \hat{S}_0(t^*))$ and $(dt^*, 0)$. Any value > 1 can be chosen for d but for numerical reasons we recommend $d = 2$. One therefore obtains

$$\hat{S}_0^e(t) = b_0 + b_1 t$$

with

$$b_0 = \hat{S}_0(t^*) \frac{d}{d-1} \quad \text{and} \quad b_1 = -\hat{S}_0(t^*) \frac{1}{t^*(d-1)}$$

Due to assumed proportional hazards also the individual survival functions,

$$\hat{S}_i(t) = \hat{S}_0(t)^{\exp(\beta x_i)} \quad (\text{for } t \leq t^*) \quad \text{and} \quad \hat{S}_i^e(t) = \hat{S}_0^e(t)^{\exp(\beta x_i)} \quad (\text{for } t > t^*)$$

are now completely defined.

3. Each censored survival time t_i^c will now be augmented to become an uncensored time t_i :

3.1. Draw a random number u_i , uniformly distributed in the interval $[0, \hat{S}_i(t_i^c)]$ with $\hat{S}_i(t_i^c) = \hat{S}_0(t_i^c)^{\exp(\beta x_i)}$

Note that cumulative survival probabilities for $t > t_i^c$ are uniformly distributed in the interval $[0, \hat{S}_0(t_i^c)]$ and that we draw u_i from one of these cumulative survival probabilities.

3.2. Calculate t_i

3.2.1. if $u_i \geq \hat{S}_i(t^*)$ then $t_i = t_j$ for which $\hat{S}_i(t_j) \geq u_i > \hat{S}_i(t_{j+1})$ (t_j denoting the ordered uncensored survival times). See the example for $u_{i,1}$ in Fig. 1.

3.2.2. if $u_i < \hat{S}_i(t^*)$ then $t_i = [\exp((\log u_i) / \exp(\beta x_i)) - b_0] / b_1$ with b_0 and b_1 calculated in step 2.

The latter expression follows from equating

$$\hat{S}_0^e(t_i)^{\exp(\beta x_i)} = (b_0 + b_1 t_i)^{\exp(\beta x_i)} \quad \text{to} \quad u_i.$$

See the example for $u_{i,2}$ in Fig. 1.

4. Calculate a measure of correlation, $\Gamma(t, x)$, for example $r_s(t, x)$ or $\tau(t, x)$, where t stands for either an observed or an imputed uncensored survival time.

5. Repeat steps 3 and 4 m times and then obtain $\bar{\Gamma}$.

In Fig. 1 it is shown schematically how a generated u_i leads to its corresponding t_i , both, for the situation where the distribution of t obeys the step function from the Cox analysis (step 3.2.1.) and where it obeys the extrapolated function (step 3.2.2.). From Fig. 1 it is also obvious that u_i has to be sampled from the range $[0, \hat{S}_i(t_i^c)]$ as $u_i > \hat{S}_i(t_i^c)$ could result in $t_i < t_i^c$.

The calculation of Γ is unaffected by monotonic transformations of survival time in general and by the specification of a monotonically decreasing function $\hat{S}_0^e(t)$ for

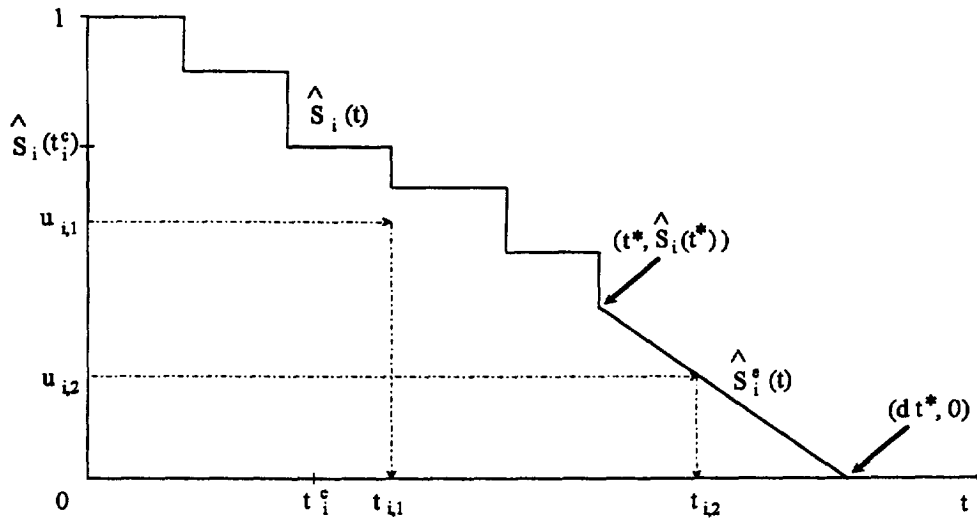


Fig.1. Schematic representation of step 3 of the algorithm.

Note that in step 3 imputed survival times (here $t_{i,1}$ and $t_{i,2}$) are obtained from random numbers $u_{i,1}$ and $u_{i,2}$, given an individual survival function, $\hat{S}_i(t)$ and $\hat{S}_i^c(t)$, a censored survival time t_i^c and the value of the survival function at t_i^c , $\hat{S}_i(t_i^c)$.

$t > t^*$ (of step 2) in particular. Only for simplicity a linear function is used. Any other monotonically decreasing function does not change the order of the resulting imputed values for t . Only this order is needed for r_s , r_{pr} or τ . However, proportional hazards are also assumed for $t > t^*$ in step 3.2.2.

The Monte Carlo component of the suggested procedure adds extra variability to the estimate of Γ but by increasing m this extra variability measured by $\text{std}(\bar{\Gamma})$ can be made arbitrarily small. In practice, m can be increased during calculations until $\text{std}(\bar{\Gamma}) < c$, c set to a small value relative to the assumed value of Γ , e.g. $c = 0.005$. We also suggest to use $\text{Min}(m) = 3$.

3. Empirical results

The performance of the suggested procedure was explored under various conditions by means of a factorial Monte Carlo study choosing exponential or lognormal distributions for survival times, underlying correlations of $r_s = 0, 0.3, 0.6, 0.9$ and 0.95 , censoring proportions of 0%, 30%, 60%, 90% and 95% and sample sizes of $n = 60, 120$ and 360 .

Values of a covariate X were sampled from a uniform distribution $[0, \sqrt{3}]$ using the random number generator G05CAF of NAG (1991). Exponential survival times with hazards $\exp(-X\theta)$ were generated using G05DBF of NAG (1991). The

Table 1

Monte Carlo study of Spearman's r_s for $n = 120$ and exponential survival times: empirical results for mean (\bar{r}_s) and corresponding $\text{std}(\text{mean}(\bar{r}_s))$

Approximate value of underlying r_s	Censoring proportions				
	0%	30%	60%	90%	95%
0					
0.3	0.00 ± 0.010	0.00 ± 0.011	0.00 ± 0.013	-0.01 ± 0.026	0.03 ± 0.037
0.6	0.29 ± 0.009	0.29 ± 0.010	0.30 ± 0.013	0.27 ± 0.020	0.29 ± 0.030
0.9	0.60 ± 0.007	0.60 ± 0.007	0.60 ± 0.010	0.60 ± 0.017	0.59 ± 0.023
0.95	0.89 ± 0.002	0.89 ± 0.002	0.89 ± 0.002	0.90 ± 0.005	0.87 ± 0.008^a
	0.95 ± 0.001	0.94 ± 0.001	0.94 ± 0.001	0.93 ± 0.003^a	0.92 ± 0.005^a

^a In these conditions calculations of r_s could not be carried out for all 100 simulated data sets. The apparent downward bias of mean (\bar{r}_s) is possibly due to the omission of samples with highest correlations and/or censoring proportions.

generation of lognormal survival times T was based on the relationship $T = \exp(\omega X + X')$ with $X' \sim N(0, 1)$ using G05DDF of NAG (1991). Parameter values of θ (0, 0.713, 1.772, 4.962, 7.419) and ω (0, 0.637, 1.495, 3.940, 5.872) which result in approximate expected values for \hat{r}_s of 0, 0.3, 0.6, 0.9 and 0.95 were obtained iteratively, using samples ('populations') of size $n = 50000$.

The generated samples were censored using the procedure by Gehan and Thomas (1969) to model a clinical trial. Individuals were assumed to enter a study at a constant rate in an interval $(0, Z)$ and then to fail according to the prescribed failure time distribution. For each experimental condition a value of Z , the time of analysis, was determined as in Lininger et al (1979) to achieve an expected 0%, 30%, 60%, 90% or 95% censoring of survival times. For each simulated data set the number of imputations m was increased individually until $\text{std}(\bar{r}_s) \leq 0.005$ was achieved.

The results of this investigation for $n = 120$, based on 100 simulated data sets each, are given in Tables 1 and 2 for exponential and lognormal survival times, respectively. Results for $n = 60$ and $n = 360$ consistently had bigger and smaller standard deviations but did not show any difference in performance otherwise. The main message from Table 1 is that the correlation of an underlying uncensored population can be estimated from censored samples without bias, even with censoring as high as 90% and for correlations of up to 0.9. Thus under proportional hazards the procedure performs satisfactorily in most situations likely to occur in practice.

While the assumption of proportional hazards – the stability of effects over time – is fulfilled in the experiments with exponential survival times, it is not in the experiments with lognormal survival times. This inevitably causes bias in the estimates of r_s since $\hat{\beta}$ obtained from Cox regression for the time period mainly covered by the samples does not extend to the time period which is covered inadequately or not at all. Magnitude of bias will of course depend on the degree of

Table 2

Monte Carlo study of Spearman's r_s for $n = 120$ and lognormal survival times: empirical results for mean (\bar{r}_s) and corresponding $\text{std}(\text{mean}(\bar{r}_s))$

Approximate value of underlying r_s	Censoring proportions				
	0%	30%	60%	90%	95%
0					
0	0.01 ± 0.010	0.00 ± 0.011	0.00 ± 0.014	0.02 ± 0.026	0.01 ± 0.034
0.3	0.30 ± 0.010	0.31 ± 0.010	0.33 ± 0.012	0.42 ± 0.019	0.51 ± 0.021
0.6	0.60 ± 0.007	0.61 ± 0.007	0.64 ± 0.008	0.74 ± 0.011	0.76 ± 0.013
0.9	0.89 ± 0.002	0.90 ± 0.002	0.90 ± 0.002	0.92 ± 0.003	0.93 ± 0.003^a
0.95	0.95 ± 0.001	0.94 ± 0.001	0.94 ± 0.001	0.95 ± 0.002^a	0.94 ± 0.002^a

^a In these conditions calculations of r_s could not be carried out for all 100 simulated data sets. A bias of mean (\bar{r}_s) due to the omission of samples with highest correlation and/or censoring proportions can be expected.

instability of effects over time and on the amount of censoring. The smaller the proportion of censored survival times to be completed by the algorithm the smaller will be the effect of nonproportional hazards on the estimated correlation. Therefore in Table 2 substantial bias was only observed for censoring proportions above 60%, the performance being satisfactory otherwise.

With increasing underlying r_s the variability of the results decreases but increases with increasing censoring.

The number of imputations m required to satisfy the condition $\text{std}(\bar{r}_s) \leq 0.005$ varied substantially within the experiment, for example for exponential survival times, $r_s = 0.9$ and censoring 30% (90%) \bar{m} was 3.5 (9.6) while for $r_s = 0.3$ and censoring 30% (90%) \bar{m} was 21.8 (208). With sample sizes of $n = 60$ and 360 the average required m further increased and decreased, respectively.

4. Real data examples

For exemplification of the suggested procedure we use the Veteran's Administration lung cancer data set published in Kalbfleisch and Prentice (1980).

In our first example the correlation of survival time and Karnofsky performance Index (KI) is analyzed for the subset of patients with histology "squamous" under standard treatment. In order to be able to demonstrate both steps of the algorithm, 3.2.1. and 3.2.2., we censor the original survival time of 411 days at day 365. The first step of the algorithm requires fitting a Cox model which resulted in $\hat{\beta} = -0.0218$ and produced values of the baseline survival function $\hat{S}_0(t)$. The survival times, the values of KI in unstandardized and standardized form as used by the procedure and the values of $\hat{S}_0(t)$ are given in Table 3. The maximum observed uncensored lifetime t^* is 314, with $\hat{S}_0(t^*) = 0.079$. Setting $d = 2$ the linear function $\hat{S}_0^e(t)$ for $t > t^*$ becomes $\hat{S}_0^e(t) = 0.159 - 0.00025t$.

Table 3

Intermediate results in the generation of three completed survival times t_i for each of the censoring times t_i^c of the lung cancer data

i	t_i	KI_i	x_i	$\hat{S}_0(t_i)$	$\hat{S}_{(x=22.667)}(t_i)$	$\hat{S}_{(x=12.667)}(t_i)$	u_i	$t_i(\text{imputed})$
1	8	40	-17.333	0.937	0.961	0.952		
2	10	20	-37.333	0.871	0.919	0.900		
3	11	70	12.667	0.802	0.874	0.846		
4	25 ^c	80	22.667	0.802	0.874	0.846	0.761	72
5	42	60	2.667	0.730	0.825	0.787		
6	72	60	2.667	0.658	0.775	0.728		
7	82	40	-17.333	0.585	0.721	0.666		
8	100 ^c	70	12.667	0.585	0.721	0.666	0.277	144
9	110	80	22.667	0.504	0.658	0.594		
10	118	70	12.667	0.426	0.595	0.524		
11	126	60	2.667	0.351	0.528	0.452		
12	144	30	-27.333	0.268	0.448	0.368		
13	228	60	2.667	0.176	0.347	0.268		
14	314	50	-7.333	0.079	0.213	0.146		
15	365 ^c	70	12.667	0.079	0.213	0.146	0.046	566.9

t_i^c denotes a censored observation.

KI: Karnofsky performance Index; all other symbols as defined in step 3 of the algorithm, Section 2.

$x_i = KI_i$ (standardized to $\bar{KI} = 0$).

Now the range of the uniform distributions for the random numbers u_i is determined for each of the three censoring times 25, 100 and 365: $[0, 0.874]$, $[0, 0.666]$, $[0, 0.146]$. For observation $i = 4$ a random number $u_4 = 0.761$ is generated and compared with the relevant conditional survival function for $KI = 80$ (or $x = 22.667$), $\hat{S}_{(x=22.667)}(t_i)$, given in Table 3. According to step 3.2.1. $t_4(\text{imputed}) = t_6 = 72$. If we had sampled $u_4 = 0.15$ then $u_4 < \hat{S}_{(x=22.667)}(t^* = 314)$ and step 3.2.2. had been chosen resulting in $t_i = [\exp((\log 0.15) / \exp(-0.0218 \cdot 22.667)) - 0.159] / (-0.00025) = 457.5$.

From $u_8 = 0.277$ a value of $t_8(\text{imputed}) = t_{12} = 144$ results according to step 3.2.1. and $\hat{S}_{(x=12.667)}(t_i)$ of Table 3. For $u_{15} = 0.046$ step 3.2.2. leads to $t_i = 566.9$. For this data set with completed survival times the Spearman correlation is $r_s = 0.165$. In accordance with a precision requirement of $\text{std}(\bar{r}_s) < 0.005$ 324 data sets with completed survival times have been required. Spearman correlations of the next 4 data sets were 0.344, 0.324, 0.279 and 0.416, respectively. The association between KI and survival time in the underlying uncensored target population is estimated from 324 data sets as $\bar{r}_s = 0.311$.

For our second example we use the complete lung cancer data set consisting of 137 patients for whom 128 uncensored and 9 censored survival times are recorded as well as potential prognostic factors such as KI and age (both continuous), treatment (dichotomous) and histology (qualitative, four levels). Results of the standard analysis of this data set by Cox's model are shown in Table 4. Our suggested technique can now be used to obtain an estimate of the proportion of the

Table 4
Analysis of the lung cancer study by a Cox model

Factors	Relative risk (CI)	p
Treatment	1.3 (0.90–2.01)	0.15
Age	0.99 (0.97–1.01)	0.34
Histology	2.3/3.2/1.5 (1.38–3.98/1.81–5.77/0.86–2.60)	< 0.001
Karnofsky Index	0.97 (0.96–0.98)	< 0.001

CI = 95% confidence interval.

variation of survival explained by the prognostic factors X of the lung cancer study. Explained variation in this sense can be expressed by $R^2 = r_s^2(t, x\hat{\beta})$ which is analogous to one of the definitions of multiple R^2 in the general linear model (cf. Kvalseth, 1985), $R^2 = r^2(y, x\hat{\beta})$, with r and y denoting Pearson correlation and dependent variable respectively. Thus an explained variation of 100% for Cox's model means that the order of survival times can be predicted perfectly. In contrast to several other measures of explained variation for Cox's model (cf. Schemper and Stare, 1996) this measure's expectation is unaffected by increasing censoring.

For a precision requirement of $\text{std}(\bar{r}_s) \leq 0.005$ and $\text{Min}(m) = 3$ three completed survival times are generated for each of the nine censoring times leading to three estimates of $r_s(t, x\hat{\beta})$: 0.652, 0.644, 0.661 with $\bar{r}_s = 0.652$. Thus approximately 42.5% of the variation of survival can be explained by a model containing KI, age, treatment and histology as covariates.

If we restrict individual follow-up to 144 days then 30% of survival times are censored. Then we obtain $\bar{r}_s = 0.678$ and $R^2 = 0.46$. The increase in explained variation is due to the fact that the proportional hazards assumption is not perfectly fulfilled for the lung cancer data and therefore using $\hat{\beta}$ beyond 144 days is not completely valid. By this example we reemphasize that users of our suggested technique should be aware of the possibly limited tenability of the proportional hazards assumption beyond the time frame covered by a sample.

5. Further remarks

We have only dealt with point estimates of nonparametric measures of association, not with respective estimates of their variability. The variance of a statistic $\hat{\theta}$ from a multiple imputed data set was defined as follows (cf. Rubin, 1991):

$$\text{Var}(\hat{\theta}) = \left(\sum_{k=1}^m \text{Var}_1(\hat{\theta}_k)/m \right) + (1 + m^{-1})\text{Var}_2(\hat{\theta}) \quad (1)$$

with $\text{Var}_1(\hat{\theta}_k)$ denoting the variance of a statistic obtained for the k th imputed data set and $\text{Var}_2(\hat{\theta})$ being the variance between the m estimates of θ . For uncensored

data the second term on the right of equation (1) vanishes while with increasing censoring this and only this term will tend to increase, making higher values of m desirable. While $\text{Var}_2(\hat{\theta})$ can easily be obtained, for $\text{Var}_1(\hat{\theta}_k)$, the non-null variance of a nonparametric correlation coefficient, still no general analytic solution is available.

We therefore recommend to use a bootstrap estimate (cf. Efron and Tibshirani, 1993) of $\text{Var}_1(\hat{\theta}_k)$ (cf. Schemper, 1987), resampling separately from each of the m imputed data sets. If $\text{Var}(\hat{\theta})$ is needed for a test of zero correlation then expressions of variances under a null hypothesis of zero correlation are known (cf. Kendall and Gibbons, 1990). Alternatively, a significant estimate of β within Cox regression, performed in step 1 of the presented algorithm, could be taken as sufficient evidence of an underlying association. We also think that supplementing results from a Cox analysis by measures of association will mainly serve descriptive purposes.

In an attempt to decrease the variability resulting from the multiple imputations, experiments were performed using smoothed survival functions as discussed by Whittemore and Keller (1986) to replace the step functions for $\hat{S}_i(t)$ in step 3.2.1. of the presented algorithm. But this refinement did not reduce the variability of results.

We have restricted attention to samples where the application of a proportional hazards model is appropriate, which is probably the majority of applications with survival data. For these situations we have demonstrated the satisfactory performance of the suggested procedure. If a linear regression relationship and in particular homoscedasticity hold then the iterative data augmentation algorithm for censored data as presented by Wei and Tanner (1991) is more appropriate. Any of the nonparametric correlation coefficients and in this case also the parametric Pearson correlation can then be calculated for the final uncensored data set.

The presented algorithm has been implemented in a SAS Macro (with files `multimp.sas` and `multimp.fortran`) which is available by ftp to `vm.akh-wien.ac.at` specifying the userid 'Biometry'.

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