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Proportional Hazards
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We consider two approaches for bias evaluation and reduction in the proportional hazards model (PHM) proposed by Cox. The first one is an analytical approach in which we derive the n^{-1} bias term of the maximum partial likelihood estimator. The second approach consists of resampling methods, namely the jackknife and the bootstrap. We compare all methods through a comprehensive set of Monte Carlo simulations for the special one parameter PHM. The results suggest that bias-corrected estimators have better finite-sample performance than the standard maximum partial likelihood estimator and there is some evidence of the bootstrap-correction superiority. Finally an application illustrates the proposed approaches.

Keywords: Bias correction; bootstrap; jackknife; Weibull regression model

1 Introduction

In the past years, special attention has been given to the proportional hazards model (PHM) proposed by Cox (1972). This model provides a flexible method for exploring the association of covariates with failure rates and for studying the effect of a covariate of interest, such as treatment, while adjusting for other covariates. It also allows for time-dependent covariates. The applications, in many instances, in which this model is used have small sample sizes. For example, in a Phase II clinical trial with 20 patients and approximately 20% censoring, the effective sample size is 16 patients.

Estimation of the coefficients of the model is based on the partial likelihood (Cox, 1975). Such estimates have biases that are typically of order n^{-1} in large samples, where n is the sample size. In small or moderate-sized samples such as the situation above, these biases can be large. It is then helpful to have rough estimates of their size and simple formulae for bias correction.

There has been considerable interest in recent years in bias evaluation and correction for the maximum likelihood estimates. In fact, the basic methodology for calculating the n^{-1} biases of the maximum likelihood estimates has been applied to nonlinear regression models with normal errors (Box, 1971; Cook *et al.*, 1986), binary response models (Sowden, 1971), logistic discrimination problems (McLachlan, 1980), generalized linear models (Cordeiro and McCullagh, 1991), generalized log-gamma regression models (Young and Bakir, 1987), nonlinear exponential family regression models (Paula, 1992), multiplicative heteroscedastic regression models (Cordeiro, 1993). However, we could not find bias correction results for the maximum likelihood estimates related to the PHM.

The purpose of this paper is to present two approaches, analytical and resampling, for bias evaluation and reduction in the PHM. The paper is outlined as follows. In Section 2, we present the PHM and the maximum partial likelihood estimator. The bias of order n^{-1} of this estimator is derived in Section 3 taking in details the one-parameter special case. In Section 4, we describe briefly the resampling techniques used, bootstrap and jackknife, moving to the simulation study of Section 5. An application illustrates the proposed approaches in Section 6.

2 The PHM

The most popular form of the proportional hazards model, for covariates not dependent on time, uses the exponential form for the relative hazard, so that the hazard function is given by

$$\lambda(t) = \lambda_0(t) \exp(Z'\beta) \tag{1}$$

where $\lambda_0(t)$, the baseline hazard function, is an unknown non-negative function of time, Z is the covariate matrix and β is a p -vector of parameters to be estimated.

Estimation of β is based on the partial log-likelihood which in the absence of ties is written for the model (1) as

$$l(\beta) = \sum_{i=1}^n \delta_i \left[(Z'_i \beta) - \log \left(\sum_{j \in R_i} \exp(Z'_j \beta) \right) \right] \quad (2)$$

where $R_i = \{k \mid t_k \geq t_i\}$ is the risk set at time t_i , $Z'_i = (z_{i1}, \dots, z_{ip})$ is the i -th line of the matrix Z , and δ_i is the failure indicator. Estimates of β are obtained by maximizing (2), that is called maximum partial likelihood estimate (MPLE), which is equivalent to solving the equations defined by the score vector

$$\sum_{i=1}^n \delta_i [z_{ik} - A_{ik}(\beta)] = 0, \quad k = 1, \dots, p, \quad (3)$$

where $A_{ik}(\beta) = \frac{\sum_{j \in R_i} [z_{jk} \exp(Z'_j \beta)]}{\sum_{j \in R_i} \exp(Z'_j \beta)}$.

The kl element of the observed information matrix is given by

$$-\frac{\partial^2 l(\beta)}{\partial \beta_k \partial \beta_l} = \sum_{i=1}^n \delta_i [B_{ikl}(\beta) - A_{ik}(\beta)A_{il}(\beta)] \quad (4)$$

where $B_{ikl}(\beta) = \frac{\sum_{j \in R_i} [z_{jk} z_{jl} \exp(Z'_j \beta)]}{\sum_{j \in R_i} \exp(Z'_j \beta)}$.

The derivatives of third order of the partial log-likelihood will be necessary to obtain the term of order n^{-1} of the bias. The klm element of this term is given by

$$\begin{aligned} \frac{\partial^3 l(\beta)}{\partial \beta_k \partial \beta_l \partial \beta_m} = & - \sum_{i=1}^n \delta_i [C_{iklm}(\beta) - A_{ik}(\beta)B_{ilm}(\beta) - A_{il}(\beta)B_{ikm}(\beta) - \\ & A_{im}(\beta)B_{ikl}(\beta) + 2A_{ik}(\beta)A_{il}(\beta)A_{im}(\beta)] \end{aligned} \quad (5)$$

where $C_{iklm}(\beta) = \frac{\sum_{j \in R_i} [z_{jk} z_{jl} z_{jm} \exp(Z'_j \beta)]}{\sum_{j \in R_i} \exp(Z'_j \beta)}$.

3 Bias of order n^{-1}

We denote the partial log-likelihood function (2) by l . We shall use the following tensor notation for mixed cumulants of the log-likelihood derivatives: $\kappa_{rs} = E \left(\frac{\partial^2 l}{\partial \beta_r \partial \beta_s} \right)$, $\kappa_{rst} =$

$E\left(\frac{\partial^3 l}{\partial \beta_r \partial \beta_s \partial \beta_t}\right)$, $\kappa_{r,s} = E\left(\frac{\partial l}{\partial \beta_r} \frac{\partial l}{\partial \beta_s}\right)$, $\kappa_{rs}^{(t)} = \frac{\partial \kappa_{rs}}{\partial \beta_t}$, and so on. The tensor notation has the advantage of being a unified notation that includes both moments and cumulants as special cases (Lawley, 1956). All κ 's refer to a total over the sample and are, in general, of order n . Note that the Fisher information matrix has elements $\kappa_{r,s} = -\kappa_{rs}$ and let $\kappa^{r,s} = -\kappa^{rs}$ denote the corresponding elements of its inverse. The mixed cumulants satisfy certain equations, which facilitate their calculations, such as $\kappa_{rst} = \kappa_{rs}^{(t)} - \kappa_{rs,t}$.

Let $B(\hat{\beta})$ be the n^{-1} bias of $\hat{\beta}$. From the general expression for the multiparameter n^{-1} biases of the maximum likelihood estimator given by Cox and Snell (1968), we can write

$$B(\hat{\beta}) = \sum \kappa^{a,r} \kappa^{t,u} (\kappa_{rtu}/2 + \kappa_{rt,u}) \quad (6)$$

where the summation is over all p parameters. A detailed discussion of this expression can be found in McCullagh (1987) and Cordeiro and McCullagh (1991).

In order to get the term of order n^{-1} of the bias in expression (6), we have to obtain some mixed cumulants of the partial log-likelihood. It means, take expectations of the derivative elements presented in Section 2. Calculation of unconditional expectations would require a fuller specification of the censoring mechanism. This information is not generally available. However, these expectations can be taken conditional on the entire history of failures and censorings up to each time t of failure. This is the way used to build the partial likelihood and allows a direct verification that the terms of l do have some of the desirable properties of the increments of the log-likelihood function.

In this way the observed and expected values of the derivatives of l taken over a single risk set are **identical** (Cox and Oakes, 1984).

In the special case of one parameter PHM, expression (6) for the bias to order n^{-1} simplifies to

$$B(\hat{\beta}) = -\frac{1}{2\kappa_{\beta\beta}^2} (\kappa_{\beta\beta\beta} - 2\kappa_{\beta\beta}^{(\beta)}) = \frac{\kappa_{\beta\beta\beta}}{2\kappa_{\beta\beta}^2} \quad (7)$$

where $\kappa_{\beta\beta} = -\sum_{i=1}^n \delta_i [B_{ikk}(\beta) - A_{ik}^2(\beta)]$ and $\kappa_{\beta\beta\beta} = -\sum_{i=1}^n \delta_i [C_{ikkk}(\beta) - 3A_{ik}(\beta)B_{ikk}(\beta) + 2A_{ik}^3(\beta)]$.

We can evaluate (7) at $\beta = \hat{\beta}$ and define a corrected estimator by

$$\tilde{\beta}_C = \hat{\beta} - \hat{B}(\hat{\beta})/n. \quad (8)$$

4 Resampling Methods

In the resampling context, two frequently used methods are: the jackknife (Quenouille, 1949, 1956) and the bootstrap (Efron, 1979; Efron and Tibshirani, 1993). The jackknife procedure may be described as follows: let β be an unknown parameter and T_1, T_2, \dots, T_n a sample of n *i.i.d.* observations with joint distribution function F_β which depends on β . Suppose that a reasonably good estimation method (but biased) is used. Indicate by $\hat{\beta}_{(i)}$, $i = 1, \dots, n$, the estimate of β obtained by removing the i -th observation, that is, $\hat{\beta}_{(i)} = \hat{\beta}(T_1, \dots, T_{i-1}, T_{i+1}, \dots, T_n)$. Let $\hat{\beta}$ be an estimate of β based on all n observations. Define the new estimates as

$$\tilde{\beta}_i = n\hat{\beta} - (n-1)\hat{\beta}_{(i)} = \hat{\beta} - (n-1)(\hat{\beta}_{(i)} - \hat{\beta}), \quad i = 1, \dots, n,$$

where $(n-1)(\hat{\beta}_{(i)} - \hat{\beta})$ is the jackknife estimate of the bias.

The bias-corrected jackknife estimate of β is then the average of the $\tilde{\beta}_i$, $i = 1, \dots, n$, that is,

$$\tilde{\beta}_J = n\hat{\beta} - (n-1)\hat{\beta}_{(\cdot)}, \quad (9)$$

where $\hat{\beta}_{(\cdot)} = \sum_{i=1}^n \hat{\beta}_{(i)}/n$. The jackknife estimate $\tilde{\beta}_J$ eliminates the term of order n^{-1} of the bias.

The (nonparametric) bootstrap procedure may be described as follows: let the parameter of interest be written as the functional $\beta = t(F)$ of the distribution function F and $\hat{\beta} = t(\hat{F})$ be its “plug-in” estimate, where \hat{F} is the empirical distribution function of the data $t = (t_1, \dots, t_n)$. The bias of $\hat{\beta}$ is defined as

$$\text{bias}_F = E_F(\hat{\beta}) - \beta = E_F(\hat{\beta}) - t(F).$$

Draw a bootstrap sample $t^* = (t_1^*, \dots, t_n^*)$ from the empirical distribution function \hat{F} . A bootstrap sample t_1^*, \dots, t_n^* is defined as a random sample of size n drawn with replacement from the original data (t_1, \dots, t_n) . The bootstrap estimate of the bias of $\hat{\beta}$ is then defined as

$$\text{bias}_{\hat{F}} = E_{\hat{F}}(\hat{\beta}^*) - t(\hat{F}),$$

where $E_{\hat{F}}(\hat{\beta}^*)$ is the expectation of $\hat{\beta}$ based on the empirical distribution function of the bootstrap sample and $t(\hat{F})$ is the “plug-in” estimate of β . The bootstrap estimate of the bias may be approximated by a Monte Carlo simulation procedure. Choose B independent bootstrap samples $t^{*1}, t^{*2}, \dots, t^{*B}$ from the empirical distribution \hat{F} . Evaluate the bootstrap replications $\hat{\beta}_b^*$, $b = 1, \dots, B$, and approximate the expectation $E_{\hat{F}}(\hat{\beta}^*)$ by $\hat{\beta}_{(\cdot)}^* = \sum_{b=1}^B \hat{\beta}_b^* / B$. The bootstrap estimate of the bias of $\hat{\beta}$, of order n^{-1} , based on the B replications is then given by

$$\text{bias}_B = \sum_{b=1}^B (\hat{\beta}_b^* / B) - \hat{\beta}.$$

Thus the (nonparametric) bootstrap bias-corrected estimate of β is

$$\tilde{\beta}_B = 2\hat{\beta} - \hat{\beta}_{(\cdot)}^*. \quad (10)$$

We remark that there is a wrong tendency to view $\hat{\beta}_{(\cdot)}^*$ as the bootstrap bias-corrected estimate (see Efron and Tibshirani, 1993, p. 138).

5 Simulation Study

In this section we perform Monte Carlo simulations comparing the performance of the usual MPLE and its corrected versions. For each experiment, we computed the following estimates: (i) the MPLE, (ii) the corrected estimate $\tilde{\beta}_C$, given by (8), (iii) the jackknife estimate $\tilde{\beta}_J$, given by (9), and (iv) the (nonparametric) bootstrap estimates $\tilde{\beta}_B$, given by (10). The simulation study is based on a Weibull regression model.

Two independent sets of independent random variables $T' = (T_1, \dots, T_n)$ and $U' = (U_1, \dots, U_n)$ are generated for each repetition and the lifetime $\min(T_i, U_i)$ and δ_i are recorded. T_i is a vector of realizations of a one-parameter Weibull $[\rho, \exp(z_i\beta)]$ and U_i , corresponding to the random censoring mechanism, is $U(0, \theta)$. The covariate z is generated once as a standard normal and it is maintained the same in all repetitions. The parameter β is set equal to 1.0 and 10,000 replications are run for each simulation. The bootstrap estimates were computed using $N = 200$ bootstrap replications. Larger values than 200 have been tried in the simulation but the results are essentially the same.

The simulations are performed for several combinations varying the sample sizes, $n = 10, 20, 30$, the proportion of censoring in the sample, $F = 0\%, 30\%, 60\%$, and the parameter $\rho = 0.2, 0.5, 1.0, 2.0$. The proportion of censoring, $P(U_i < T_i)$, is obtained by controlling the value of the parameter θ . Table I displays the simulations sample means and the root of the mean square error (RMSE) for all four estimators.

As expected, the bias of the MPLE increases when the sample size n decreases or when the proportion of censoring F increases. In general, the bias increases as the shape parameter of the Weibull distribution increases. It can be observed that the bias is really large for $F = 60\%$ and $n = 10$.

From Table I, it seems that there is a minor bias reduction using the corrected estimator $\tilde{\beta}_C$ when compared with the standard MPLE. The reduction is bigger in the worst cases presented in the simulations. A similar reduction happens with the mean square error and that is an indication of no variance inflation when using the corrected estimator $\tilde{\beta}_C$.

Regarding the resampling methods, in most of the cases tested, they had a better performance over the analytical estimators $\hat{\beta}$ and $\tilde{\beta}_C$. Excepting those cases with very high censoring proportion ($F = 60\%$) and very low sample sizes ($n = 10$), the bias reduction and the RMSE reduction were noticeable. These conclusions are consistent with the recent results reported by Ferrari and Silva (1997), in which simulation studies demonstrated that jackknife and bootstrap methods for bias correction may not work properly with very low sample sizes. The bootstrap bias corrected estimator $\tilde{\beta}_B$ is better than the jackknife $\tilde{\beta}_J$ in terms of bias reduction and it has the smallest RMSE. It seems that $\tilde{\beta}_B$ outperforms $\tilde{\beta}_C$ except in the critical situations $F = 60\%$ and $n = 10$.

6 Illustrative Example

Feigl and Zelen (1965) presented a data set of survival times of 17 leukemia patients. The response t is time to death measured in weeks from diagnosis and a covariate z is \log_{10} of initial white blood cell count. The association between t and z is the main aspect of interest.

Table I: Sample Means and Mean Square Error Root

ρ	F	n	$\hat{\beta}$	RMSE	$\tilde{\beta}_C$	RMSE	$\tilde{\beta}_J$	RMSE	$\tilde{\beta}_B$	RMSE
0.2	0	10	1.135	2.567	1.119	2.541	0.836	2.521	0.845	2.122
		20	1.025	1.363	1.020	1.361	0.987	1.303	0.975	1.280
		30	1.040	1.069	1.039	1.069	0.994	1.035	1.000	1.031
	30	10	1.240	3.132	1.212	3.052	0.689	3.399	0.857	2.741
		20	1.097	1.572	1.089	1.567	0.972	1.394	0.960	1.403
		30	1.054	1.229	1.053	1.228	0.991	1.161	0.995	1.169
	60	10	1.683	5.445	1.570	4.950	0.568	7.885	1.314	5.754
		20	1.281	2.383	1.265	2.367	0.785	2.150	0.828	2.006
		30	1.114	1.679	1.111	1.675	0.969	1.508	0.964	1.508
0.5	0	10	1.173	1.137	1.159	1.120	0.829	1.245	0.864	0.952
		20	1.068	0.600	1.064	0.598	0.985	0.567	0.989	0.553
		30	1.048	0.464	1.048	0.464	0.997	0.450	1.005	0.448
	30	10	1.264	1.571	1.239	1.505	0.654	2.140	0.916	1.538
		20	1.104	0.735	1.099	0.732	0.959	0.649	0.960	0.638
		30	1.059	0.539	1.058	0.539	0.992	0.510	0.998	0.508
	60	10	1.482	2.584	1.402	2.305	0.604	4.045	1.240	2.872
		20	1.239	1.247	1.226	1.206	0.838	1.188	0.891	1.076
		30	1.099	0.762	1.097	0.760	0.966	0.669	0.964	0.665
1.0	0	10	1.182	0.760	1.167	0.740	0.769	0.919	0.865	0.675
		20	1.072	0.383	1.069	0.382	0.978	0.360	0.980	0.344
		30	1.044	0.283	1.043	0.283	0.995	0.275	1.000	0.271
	30	10	1.301	1.185	1.270	1.099	0.632	1.947	1.011	1.312
		20	1.110	0.494	1.106	0.491	0.956	0.440	0.952	0.417
		30	1.059	0.335	1.058	0.334	0.989	0.315	0.994	0.308
	60	10	1.473	1.762	1.381	1.519	0.802	3.060	1.359	2.095
		20	1.238	0.916	1.224	0.847	0.818	1.108	0.914	0.855
		30	1.103	0.491	1.101	0.489	0.952	0.423	0.953	0.411
2.0	0	10	1.231	0.806	1.207	0.761	0.639	1.406	0.946	0.919
		20	1.072	0.319	1.069	0.317	0.960	0.296	0.951	0.276
		30	1.040	0.223	1.039	0.222	0.989	0.215	0.991	0.208
	30	10	1.348	1.076	1.298	0.958	0.715	2.001	1.177	1.328
		20	1.109	0.416	1.105	0.412	0.923	0.389	0.920	0.352
		30	1.056	0.268	1.055	0.267	0.975	0.248	0.974	0.236
	60	10	1.429	1.247	1.321	1.032	1.101	2.280	1.433	1.580
		20	1.220	0.758	1.207	0.708	0.774	1.219	0.933	0.784
		30	1.113	0.418	1.110	0.416	0.909	0.427	0.923	0.357

Table II: Point and 95% Confidence Estimates for the Example Data

	$\hat{\beta}$	$\tilde{\beta}_C$	$\tilde{\beta}_J$	$\tilde{\beta}_B$
Estimate	-1.406	-1.404	-0.569	-0.963
S.E.	0.488	0.488	-	-
CI	(-2.36,-0.45)	(-2.36,-0.45)	(-4.88,19.5)	(-2.59,1.23)

Table II displays the estimates for the parameter β associated with covariate z and their respective 95% confidence intervals (CI). Jackknife and bootstrap confidence intervals are built in terms of their empirical percentiles. As expected, MPLE $\hat{\beta}$ is very close to the corrected estimate $\tilde{\beta}_C$ but it is not close to resampling bias corrected estimates. According to the simulation results obtained in Section 5, $\tilde{\beta}_B$ is in general the less biased estimate among those considered in the study. It seems to be in agreement to the analysis performed by Cox and Snell (1981) using an exponential regression model. They obtained an estimate of -1.109 for β and $\tilde{\beta}_B$ is the closest estimate to this value.

On the other hand, the confidence interval based on the bootstrap has length wider than those based on $\hat{\beta}$ and $\tilde{\beta}_C$. The main reason might be the asymmetric distributions of the survival times. It can also be observed the disagreement between these estimates in judging the importance of the covariate to explain the response in a significance level of 0.05. Jackknife confidence interval is not appropriate since it is based on just 17 resamples.

7 Final Remarks

The main purpose of this paper is to present analytical and resampling methods for bias evaluation and reduction in the PHM proposed by Cox (1972), a model that has been useful in a considerable number of practical applications. Conducted for the special one parameter PHM, our simulation results suggest that bias-corrected estimates have better performance than the standard maximum partial likelihood estimates. Although computationally intensive, resampling methods may be an attractive alternative for bias reduction, avoiding the sophisticated mathematics commonly present in analytical methods. In particular, we show some evidence that the bootstrap is superior than the jackknife-corrected estimate.

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