A Monte Carlo simulation study: The number of minimum events required in Firth's penalized partial likelihood approach in Cox regression models

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10/26/2018

Contents

Introduction

Issue of Real Data

(Breast Cancer With Low Oncotype DX Recurrence Score)

Oncotype RS	Survival	Censor	event
1-10	OS	107	0
11-<18		220	5
1-10	DFS	95	12
11-<18		215	10
1-10	DM	107	0
11-<18		224	1

Table 1 Univariate Survival Analysis of OS

			OS(Months)		
Covariate	**Level**	**N**	**Hazard Ratio (95% CI)**	**HR P-value**	**Log-rank P-value**
Oncotype_RS_	11-<18	225	16259017 (0.00-.)	0.995	0.136
	1-10	107	-	-	

Table 2 Univariate Survival Analysis of DFS

			DFS(Months)		
Covariate	**Level**	**N**	**Hazard Ratio (95% CI)**	**HR P-value**	**Log-rank P-value**
Oncotype_RS_	11-<18	225	0.53 (0.22-1.26)	0.148	0.142
	1-10	107	-	-	

Introduction

- Cox models probably lead to biased estimation of regression coefficients when survival dataset has too few outcome events.
- The phenomenon of monotone likelihood occurs in the fitting process of a Cox model when at least one parameter estimation diverges to $\pm\infty$.
- Monotone likelihood is mainly observed in datasets with rare events.
- Firth’s penalized partial likelihood Cox regression mode to analyze survival dataset with rare events.

Simulation Design

- distribution of independent: continuous (normal/exponential)

  dichotomous (degree of unbalance 1:1 1:3 1:4)

- Sample size   (20, 40, 60, 80, 100, 150, 200).

- Proportion of event (10%, 20%, 30%, and 40%).

- effect sizes of Hazard ratio 1.22, 1.86, and 3.00 (small 0.2, medium 0.62, and large 1.1).
- each combination of conditions, 1000 replication were taken.

Simulation Design

- **Performance of Firth correction approach was assessed**:

Signed percent relative bias (**accuracy**): $100\left(\bar{\hat{\beta}} - \beta\right)/\beta$

Empirical simulation variance: $\sum\left(\hat{\beta} - \beta\right)^2/(m-1)$

Model variance: $\sum Se^2/m$

Ratio (**precision**) : Empirical simulation variance/model variance ≈ 1

Percentage of failed converged of model (%) :

Results

Table 1 parameters of estimation for Larger effect size (β=1.10 HR=3.00, covariate =**normal distribution**)

Proportion event	n	$\hat{\beta}$	$\left(\bar{\hat{\beta}}-\beta\right)/\beta$ (%)	$\sum Se^2/m$ (1)	$\sum\left(\hat{\beta}-\beta\right)^2/(m-1)$ (2)	Ratio (1)/(2)	Failed converged (%)
10%	20	0.96	13.0	2.20	1.37	1.61	6.6 (57/861)
	40	1.10	0.0	1.26	1.03	1.22	1.1(11/991)
	60	1.12	1.8	0.53	0.51	1.04	0.2 (2/999)
	80	1.13	2.7	0.35	0.32	1.09	0.0(0/1000)
	100	1.10	0.0	0.24	0.22	1.09	0.0(0/1000)
	150	1.11	0.9	0.15	0.15	1.00	0.0(0/1000)
	200	1.10	0.0	0.11	0.11	1.00	0.0(0/1000)
20%	20	1.08	1.8	1.25	0.97	1.29	1.0(10/988)
	40	1.11	0.9	0.38	0.38	1.00	0.0(0/1000)
	60	1.12	1.8	0.21	0.25	0.84	0.0(0/1000)
	80	1.11	0.9	0.14	0.15	0.93	0.0(0/1000)
	100	1.10	0.0	0.11	0.11	1.00	0.0(0/1000)
	150	1.10	0.0	0.07	0.07	1.00	0.0(0/1000)
	200	1.10	0.0	0.05	0.05	1.00	0.0(0/1000)
30%	20	1.15	4.5	0.77	0.71	1.08	0.3(3/1000)
	40	1.11	0.9	0.23	0.24	0.96	0.0(0/1000)
	60	1.11	0.9	0.13	0.15	0.87	0.0(0/1000)
	80	1.11	0.9	0.09	0.09	1.00	0.0(0/1000)
	100	1.10	0.0	0.07	0.07	1.00	0.0(0/1000)
	150	1.10	0.0	0.05	0.05	1.00	0.0(0/1000)
	200	1.10	0.0	0.03	0.03	1.00	0.0(0/1000)
40%	20	1.13	2.7	0.47	0.45	1.04	0.2(2/1000)
	40	1.11	0.9	0.16	0.16	1.00	0.0(0/1000)
	60	1.11	0.9	0.10	0.10	1.00	0.0(0/1000)
	80	1.10	0.0	0.07	0.07	1.10	0.0(0/1000)
	100	1.10	0.0	0.05	0.05	1.00	0.0(0/1000)
	150	1.10	0.0	0.03	0.03	1.00	0.0(0/1000)
	200	1.10	0.0	0.02	0.02	1.00	0.0(0/1000)

Table 2 parameters of estimation for Larger effect size (β=1.10 HR=3.00, covariate =exponential distribution)

Proportion event	n	$\hat{\beta}$	$\left(\bar{\hat{\beta}}-\beta\right)/\beta$ (%)	$\sum Se^2/m$ (1)	$\sum(\hat{\beta}-\beta)^2/(m-1)$ (2)	Ratio (1)/(2)	Failed converged (%)
10%	20	0.85	22.7	71.88	30.98	2.3	16.5(143/865)
	40	1.02	7.3	2.32	1.48	1.6	2.1(21/986)
	60	1.09	0.9	0.92	0.79	1.3	0.1(1/999)
	80	1.12	1.8	0.43	0.33	1.2	0.0(0/1000)
	100	1.12	1.8	0.30	0.26	1.1	0.1(1/1000)
	150	1.11	0.9	0.17	0.15	1.1	0.0(0/1000)
	200	1.11	0.9	0.11	0.11	1.0	0.0(0/1000)
20%	20	1.10	0.0	2.95	2.01	1.5	5.1(50/987)
	40	1.12	1.8	0.48	0.36	1.3	0.0(0/1000)
	60	1.13	2.7	0.25	0.24	1.0	0.0(0/1000)
	80	1.11	0.9	0.16	0.16	1.0	0.0(0/1000)
	100	1.11	0.9	0.12	0.12	1.0	0.0(0/1000)
	150	1.10	0.0	0.07	0.07	1.0	0.0(0/1000)
	200	1.11	0.9	0.05	0.05	1.0	0.0(0/1000)
30%	20	1.20	9.1	1.31	1.27	1.1	0.9(9/997)
	40	1.13	2.7	0.27	0.25	1.1	0.0(0/1000)
	60	1.13	2.7	0.15	0.15	1.0	0.0(0/1000)
	80	1.12	1.8	0.10	0.10	1.0	0.0(0/1000)
	100	1.11	0.9	0.08	0.08	1.0	0.0(0/1000)
	150	1.11	0.9	0.05	0.05	1.0	0.0(0/1000)
	200	1.11	0.9	0.03	0.03	1.0	0.0(0/1000)
40%	20	1.18	7.3	0.70	0.66	1.1	0.1(1/999)
	40	1.14	3.6	0.18	0.17	1.1	0.0(0/1000)
	60	1.14	3.6	0.10	0.10	1.0	0.0(0/1000)
	80	1.12	1.8	0.07	0.07	1.0	0.0(0/1000)
	100	1.12	1.8	0.06	0.06	1.0	0.0(0/1000)
	150	1.11	0.9	0.03	0.03	1.0	0.0(0/1000)
	200	1.11	0.9	0.02	0.02	1.0	0.0(0/1000)

Table 3 parameters of estimation for Larger effect size (β=1.10 HR=3.00, covariate =Bernolli distribution **ratio=1:1**)

Proportion event	n	$\hat{\beta}$	$\left(\bar{\hat{\beta}}-\beta\right)/\beta$ (%)	$\sum Se^2/m$ (1)	$\sum\left(\hat{\beta}-\beta\right)^2/(m-1)$ (2)	Ratio (1)/(2)	Failed converged (%)
10%	20	0.95	13.6	2.47	1.16	2.1	41.2(326/791)
	40	1.05	4.5	1.82	1.06	1.7	11.6(113/976)
	60	1.10	0.0	1.29	0.88	1.5	3.5(35/996)
	80	1.12	1.8	0.91	0.67	1.4	0.4(4/1000)
	100	1.12	1.8	0.67	0.55	1.2	0.2(2/1000)
	150	1.12	1.8	0.40	0.36	1.1	0.0(0/1000)
	200	1.13	2.7	0.29	0.28	1.0	0.0(0/1000)
20%	20	1.06	3.6	1.93	1.04	1.9	13.5(129/958)
	40	1.12	1.8	0.94	0.64	1.5	0.7(7/1000)
	60	1.14	3.6	0.57	0.51	1.1	0.0(0/999)
	80	1.11	0.9	0.38	0.35	1.1	0.0(0/1000)
	100	1.12	1.8	0.29	0.30	1.0	0.0(0/1000)
	150	1.10	0.0	0.18	0.18	1.0	0.0(0/1000)
	200	1.12	1.8	0.13	0.13	1.0	0.0(0/1000)
30%	20	1.17	6.4	1.47	0.93	1.6	2.4(24/991)
	40	1.15	4.5	0.58	0.49	1.2	0.0(0/1000)
	60	1.14	3.6	0.34	0.34	1.0	0.0(0/1000)
	80	1.12	1.8	0.24	0.23	1.0	0.0(0/1000)
	100	1.13	2.7	0.19	0.20	1.0	0.0(0/1000)
	150	1.10	0.0	0.12	0.12	1.0	0.0(0/1000)
	200	1.11	0.9	0.09	0.09	1.0	0.0(0/1000)
40%	20	1.20	9.1	1.08	0.74	1.5	0.1(1/1000)
	40	1.16	5.5	0.41	0.36	1.1	0(0/1000)
	60	1.15	4.5	0.25	0.25	1.0	0(0/1000)
	80	1.12	1.8	0.18	0.18	1.0	0(0/1000)
	100	1.12	1.8	0.14	0.14	1.0	0(0/1000)
	150	1.11	0.9	0.09	0.09	1.0	0(0/1000)
	200	1.12	1.8	0.07	0.07	1.0	0(0/1000)

Table 4 parameters of estimation for Larger effect size (β=1.10 HR=3.00, covariate =Bernolli distribution **ratio=1:3**)

Proportion event	N	$\hat{\beta}$	$\left(\bar{\hat{\beta}}-\beta\right)/\beta$ (%)	$\sum Se^2/m$ (1)	$\sum(\hat{\beta}-\beta)^2/(m-1)$ (2)	Ratio (1)/(2)	Failed converged (%)
10%	20	1.33	20.9	∞	8.11	∞	50.5(343/679)
	40	1.29	17.3	∞	5.68	∞	19.4(185/953)
	60	1.33	20.9	∞	5.10	∞	5.5(55/992)
	80	1.28	16.4	∞	2.97	∞	1.0(10/999)
	100	1.17	6.4	0.85	0.62	1.4	0.4(4/999)
	150	1.14	3.6	0.53	0.46	1.2	0.0(0/999)
	200	1.15	4.5	0.37	0.35	1.1	0.0(0/1000)
20%	20	1.31	19.1	∞	3.62	∞	23.5(208/885)
	40	1.27	15.5	∞	2.97	∞	2.4(24/996)
	60	1.20	9.1	0.73	0.61	1.2	0.1(1/1000)
	80	1.15	4.5	0.50	0.44	1.1	0.0(0/999)
	100	1.14	3.6	0.37	0.34	1.1	0.0(0/1000)
	150	1.12	1.8	0.23	0.23	1.0	0.0(0/999)
	200	1.12	1.8	0.17	0.17	1.0	0.0(0/1000)
30%	20	1.35	22.7	∞	2.99	∞	10.6(102/960)
	40	1.20	9.1	0.79	0.59	1.3	0.3(3/1000)
	60	1.19	8.2	0.44	0.39	1.1	0.0(0/1000)
	80	1.15	4.5	0.31	0.30	1.0	0.0(0/1000)
	100	1.14	3.6	0.24	0.24	1.0	0.0(0/1000)
	150	1.14	3.6	0.15	0.15	1.0	0.0(0/1000)
	200	1.14	3.6	0.11	0.11	1.0	0.0(0/1000)
40%	20	1.34	21.8	∞	1.65	∞	5.5(54/987)
	40	1.21	10.0	0.54	0.43	1.3	0.1(1/1000)
	60	1.20	9.1	0.31	0.28	1.1	0.0(0/1000)
	80	1.16	5.5	0.22	0.21	1.0	0.0(0/1000)
	100	1.14	3.6	0.17	0.17	1.0	0.0(0/1000)
	150	1.14	3.6	0.11	0.11	1.0	0.0(0/1000)
	200	0.14	3.6	0.08	0.08	1.0	0.0(0/1000)

Table 5 parameters of estimation for Larger effect size (β=1.10 HR=3.00, covariate =Bernolli distribution **ratio=1:4**)

Proportion event	N	$\hat{\beta}$	$\left(\bar{\hat{\beta}}-\beta\right)/\beta$ (%)	$\sum Se^2/m$ (1)	$\sum(\hat{\beta}-\beta)^2/(m-1)$ (2)	Ratio (1)/(2)	Failed converged (%)
10%	20	1.67	51.8	∞	16.01	∞	52.6(339/645)
	40	1.72	56.4	∞	16.98	∞	22.4(211/944)
	60	1.31	19.1	∞	2.90	∞	7.4(73/989)
	80	1.25	13.6	∞	1.86	∞	1.6(16/997)
	100	1.18	7.3	1.02	0.71	1.4	0.7(7/997)
	150	1.14	3.6	0.63	0.54	1.2	0.0(0/1000)
	200	1.15	4.5	0.44	0.42	1.0	0.0(0/1000)
20%	20	1.38	25.5	∞	4.68	∞	27.2(235/863)
	40	1.37	24.5	∞	5.29	∞	3.2(32/995)
	60	1.22	10.9	0.87	0.68	1.3	0.3(3/1000)
	80	1.16	5.5	0.59	0.51	1.2	0.0(0/1000)
	100	1.14	3.6	0.45	0.40	1.1	0.0(0/1000)
	150	1.13	2.7	0.27	0.27	1.0	0.0(0/1000)
	200	1.14	3.6	0.19	0.19	1.0	0.0(0/1000)
30%	20	1.48	34.5	∞	5.55	∞	14.4(135/941)
	40	1.23	11.8	0.93	0.70	1.3	0.7(7/1000)
	60	1.21	10.0	0.54	0.50	1.1	0.0(0/999)
	80	1.16	5.5	0.37	0.35	1.1	0.0(0/1000)
	100	1.15	4.5	0.28	0.28	1.0	0.0(0/1000)
	150	1.14	3.6	0.17	0.17	1.0	0.0(0/1000)
	200	1.14	3.6	0.13	0.13	1.0	0.0(0/1000)
40%	20	1.40	27.3	∞	2.84	∞	8.4(82/974)
	40	1.24	12.7	0.65	0.53	1.2	0.3(3/1000)
	60	1.23	11.8	0.37	0.34	1.1	0.0(0/1000)
	80	1.16	5.5	0.26	0.25	1.0	0.0(0/1000)
	100	1.15	4.5	0.20	0.20	1.0	0.0(0/1000)
	150	1.15	4.5	0.12	0.12	1.0	0.0(0/1000)
	200	1.14	3.6	0.09	0.09	1.0	0.0(0/1000)

Key Findings

- Increasing the # of sample size and # of events alleviated non-convergence and resulted in more stable parameter estimates.
- The accuracy and precision of regression coefficient depend on both number of events and sample size, and they depend more on number of events.
- continuous covariates, the results of simulation are almost the same no matter the distribution of covariates. The minimum # events is 6-8, Sample Size>=40.
- Binary covariates, the more unbalance of category, the more chance of failed converged. And the more events and sample size are required. The minimum # events is 6-8 for low prevalence of category. Accuracy and precision of regression coefficient depend more on events than sample size.
- For multiple Cox regression model

Vittinghoff E et al suggested that 10 EPV was used in Cox model.

SAS macro on backward selection for multivariate Firth's correction Cox model

- SAS Macro (FirthPhreg_sel v1): %FirthPhreg_sel
- So far, SAS has no backward selection methods on multivariate data analysis.

- MYELOMA STUDY EXAMPLE

The example dataset uses multiple myeloma study data from Krall, Uthoff, and Harley (Krall et al., 1975) (SAS Institute Inc, 2017) in which 65 patients were treated with alkylating agents. Of those patients, 48 of 65 patients died during the study and 17 survived after the study.

Time: the survival time in months from diagnosis to death or last follow up.

VStatus: survival status, 0 = Dead, 1 = Death.

other covariates LogBUN, HGB, Platelet, Age, LogWBC, Frac, LogPBM, Protein, and SCalc at diagnosis. The detailed information can be found in SAS User's Guide . To show Firth's correction method

SAS macro

```
Title 'Table 1 Multivariate Cox Regression with Firth Correction for Survival ';

%FirthPhreg_sel (DSN =  Myeloma2,
            EVENT= Time,
            CENSOR=Vstatus,
            VAR=LogBUN HGB Contrived,
            CVAR=Contrived(desc),
            INC=0,
            ALPHA= 0.2,
            TYPE3= t,
            DEBUG=t,
            OUTPATH=&dir.\,
            FILENAME=Multivariable Firth);
Title;
```

SAS macro

Table 1 Multivariate Cox Regression with Firth Correction for Survival

Covariate	Level	Survival Time --- Hazard Ratio (95% CI)	HR P-value	Type3 P-value
LogBUN		5.53 (1.79-17.57)	**0.003**	**0.003**
hgb		0.90 (0.79-1.01)	0.066	0.066
Contrived	<=65	15.60 (.-12193.44)	**0.006**	**0.006**
	>65	-	-	

* Number of observations in the original data set = 65. Number of observations used = 65.
** Firth correction Backward selection with an alpha level of removal of 0.2 was used. No variables were removed from the model.

Reference

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Thanks!

Questions