

PH 716 Applied Survival Analysis

Part V: Cox Proportional Hazards Model

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2024/Mar/23 22:54:34

Assumptions for Cox proportional hazards (PH) model

- Observed $\tilde{T}_i = \tilde{t}_i$ and $\Delta_i = \delta_i$ (event indicator)
- T_i are independent across i , given x_{i1}, \dots, x_{ip}
- The independent and non-informative censoring
- $\lambda_{T_i}(t) = \lambda(t \mid x_{i1}, \dots, x_{ip}) = \lambda_0(t) \exp(\sum_{j=1}^p x_{ij}\beta_j)$, or equiv. $\ln \lambda_{T_i}(t) = \ln \lambda_0(t) + \sum_{j=1}^p x_{ij}\beta_j$
 - $\lambda_0(t)$ (the baseline hazard): obtained when all covariates are zeros and left unspecified
 - * A semi-parametric generalized linear model: nonparametric baseline hazard + parametric proportion
 - Proportional hazards: the HR between any two individuals, say $\lambda_{T_{i_1}}(t)/\lambda_{T_{i_2}}(t) = \exp(\sum_{j=1}^p x_{i_1j}\beta_j - \sum_{j=1}^p x_{i_2j}\beta_j)$, is constant over time
 - No intercept β_0
 - Interpretation of β_j : $\exp(\beta_j)$ is the HR associated with one-unit change of the j th covariate, fixing everything else

Weibull regression as a special case of PH models

- Recall the Weibull regression: $\ln T_i = \beta_0 + \sum_{j=1}^p x_{ij}\beta_j + \sigma\varepsilon_i$ with $\varepsilon_i \stackrel{\text{iid}}{\sim} F_{\varepsilon_i}(\epsilon) = 1 - \exp(-\exp \epsilon)$
 - $S_{T_i}(t) = \exp[-\{t/\exp(\beta_0 + \sum_{j=1}^p x_{ij}\beta_j)\}^{1/\sigma}] \Rightarrow \lambda_{T_i}(t) = (1/\sigma)t^{1/\sigma-1} \exp\{(-\beta_0 - \sum_{j=1}^p x_{ij}\beta_j)/\sigma\}$
- $\lambda_{T_i}(t) = \lambda_0(t) \exp(\sum_{j=1}^p x_{ij}\beta_j^*)$ if $\lambda_0(t) = (1/\sigma)t^{1/\sigma-1} \exp(-\beta_0/\sigma)$ and $\beta_j^* = -\beta_j/\sigma$, $j = 1, \dots, p$
- The only continuous-time model that is both a PH and an AFT model

Partial likelihood (assuming no tied failure time)

- The observed-data likelihood $L(\beta, \lambda_0) = \prod_i \lambda_{T_i}(\tilde{t}_i)^{\delta_i} S_{T_i}(\tilde{t}_i)$ relying on both $\beta = [\beta_1, \dots, \beta_p]^\top$ and unspecified $\lambda_0(\cdot)$
- Further assumptions
 - K and only K distinct, ordered failure times, say $t_1 < \dots < t_K$
 - No tied failure time: for each k , there is one and only one individual, say subject i_k , who fails at t_k
 - Risk set $\mathcal{R}(t) = \{i : \tilde{T}_i \geq t\}$: the set of individuals who are known to survive just prior to time t
- Rephrase $L(\beta, \lambda_0)$:

$$L(\beta, \lambda_0) = \prod_{i=1}^n \lambda_{T_i}(\tilde{t}_i)^{\delta_i} S_{T_i}(\tilde{t}_i) = \prod_{i=1}^n \left\{ \frac{\lambda_{T_i}(\tilde{t}_i)}{\sum_{\ell \in \mathcal{R}(\tilde{t}_i)} \lambda_{T_\ell}(\tilde{t}_i)} \right\}^{\delta_i} \times \left\{ \sum_{\ell \in \mathcal{R}(\tilde{t}_i)} \lambda_{T_\ell}(\tilde{t}_i) \right\}^{\delta_i} \times S_{T_i}(\tilde{t}_i)$$

- Take the partial likelihood (i.e., the first term of the above $L(\beta, \lambda_0)$)

$$pL(\beta) = \prod_{i=1}^n \left\{ \frac{\lambda_{T_i}(\tilde{t}_i)}{\sum_{k \in \mathcal{R}(\tilde{t}_i)} \lambda_{T_k}(\tilde{t}_i)} \right\}^{\delta_i} = \prod_{i=1}^n \left\{ \frac{\exp(\sum_{j=1}^p x_{ij} \beta_j)}{\sum_{\ell \in \mathcal{R}(\tilde{t}_i)} \exp(\sum_{j=1}^p x_{\ell j} \beta_j)} \right\}^{\delta_i} = \prod_{k=1}^K \frac{\exp(\sum_{j=1}^p x_{i_k j} \beta_j)}{\sum_{\ell \in \mathcal{R}(t_k)} \exp(\sum_{j=1}^p x_{\ell j} \beta_j)}$$

as a surrogate of $L(\beta, \lambda_0)$ in estimating β

- Cox (1972) argued that $pL(\beta)$ contained almost all the information about β
- Extensive evidence, both theoretical and numerical, supported this argument in the past few decades
- $\frac{\exp(\sum_{j=1}^p x_{i_k j} \beta_j)}{\sum_{\ell \in \mathcal{R}(t_k)} \exp(\sum_{j=1}^p x_{\ell j} \beta_j)}$: the probability of selecting a particular person (here subject i_k) from the risk set at time t_k
- Log-partial likelihood

$$p\ell(\beta) = \ln pL(\beta) = \sum_{k=1}^K \left\{ \sum_{j=1}^p x_{k j} \beta_j - \ln \sum_{\ell \in \mathcal{R}(t_k)} \exp \left(\sum_{j=1}^p x_{\ell j} \beta_j \right) \right\}$$

Ex. 5.1 The calculation of partial likelihood

i	\tilde{t}_i	δ_i	x_i
1	9	1	4
2	8	0	5
3	6	1	7
4	10	1	3

- Follow the following definition (without reordering failure times) and fill in the table

$$pL(\beta) = \prod_{i=1}^n \left\{ \frac{\exp(\sum_{j=1}^p x_{ij} \beta_j)}{\sum_{\ell \in \mathcal{R}(\tilde{t}_i)} \exp(\sum_{j=1}^p x_{\ell j} \beta_j)} \right\}^{\delta_i}$$

i	\tilde{t}_i	δ_i	x_i	$\mathcal{R}(\tilde{t}_i)$	$\left\{ \frac{\exp(x_i \beta)}{\sum_{\ell \in \mathcal{R}(\tilde{t}_i)} \exp(x_{\ell} \beta)} \right\}^{\delta_i}$
1	9	1	4		
2	8	0	5		
3	6	1	7		
4	10	1	3		

Ex. 5.2 The calculation of partial likelihood: comparison of two groups

- Covariate x_i indicating the group label

i	\tilde{t}_i	δ_i	x_i	$\mathcal{R}(\tilde{t}_i)$	$\frac{\exp(x_i \beta)}{\sum_{\ell \in \mathcal{R}(\tilde{t}_i)} \exp(x_{\ell} \beta)}$
1	4	0	0		
2	7	1	0		
3	8	0	0		
4	9	1	0		

i	\tilde{t}_i	δ_i	x_i	$\mathcal{R}(\tilde{t}_i)$	$\frac{\exp(x_i\beta)}{\sum_{\ell \in \mathcal{R}(\tilde{t}_i)} \exp(x_\ell\beta)}$
5	10	0	0		
6	3	1	1		
7	5	1	1		
8	5	0	1		
9	6	1	1		
10	8	0	1		

```
library(survival)
data = data.frame(
  tte = c(4,7,8,9,10,3,5,5,6,8),
  delta = c(0,1,0,1,0,1,1,0,1,0),
  x = c(0,0,0,0,0,1,1,1,1,1)
)
fit = coxph(Surv(tte,delta)~x, data = data)
summary(fit)
```

- $\exp(\beta)$ is the hazard ratio of $group = 1$ against $group = 0$, fixing covariates other than (if any). It implies that one jumps from $group = 0$ to $group = 1$ the hazard would be inflated by $(\exp(\beta) - 1) \times 100\%$.
- Is there any difference between the survival of the two groups? There are at least four p -values. Which one shall we refer to?
- What are meanings of other digits in the output?
- What if there are more covariates?

Ex. 5.3. Leukemia data (with tied event/failure times)

```
survival::leukemia
```

Partial likelihood (Cox's modification)

- Assumptions
 - K and only K distinct, ordered failure times, say $t_1 < \dots < t_K$
 - d_k failures at time t_k : there are d_k individuals, say subject $i_{k,1}, \dots, i_{k,d_k}$, who fail at t_k
- Accordingly

$$pL(\beta) = \prod_{k=1}^K \frac{\prod_{i \in \{i_{k,1}, \dots, i_{k,d_k}\}} \exp(\sum_j x_{ij}\beta_j)}{\sum_{D(d_k) \subset \mathcal{R}(t_k)} \prod_{i \in D(d_k)} \exp(\sum_j x_{ij}\beta_j)}$$

- $D(d_k) \subset \mathcal{R}(t_k)$: a subset of $\mathcal{R}(t_k)$ containing d_k subjects, i.e., a set of d_k individuals who are at risk at t_k
- Labeled as `exact` by `survival::coxph`

Partial likelihood (Breslow's approximation)

- Keeping the assumptions for the Cox's modification
- Substituting $\{\sum_{\ell \in \mathcal{R}(t_k)} \exp(\sum_{j=1}^p x_{\ell j}\beta_j)\}^{d_k}$ for the denominator of the Cox's modification

$$pL(\beta) = \prod_{k=1}^K \frac{\prod_{i \in \{i_{k,1}, \dots, i_{k,d_k}\}} \exp(\sum_j x_{ij}\beta_j)}{\{\sum_{\ell \in \mathcal{R}(t_k)} \exp(\sum_{j=1}^p x_{\ell j}\beta_j)\}^{d_k}}$$

- Default tie-handling method in SAS

Partial likelihood (Efron's approximation)

- Keeping the assumptions for the Cox's modification
- Substitute $\prod_{m=1}^{d_k} \{\sum_{\ell \in \mathcal{R}(t_k)} \exp(\sum_{j=1}^p x_{\ell j} \beta_j) - \frac{m-1}{d_k} \sum_{i \in \{i_{k,1}, \dots, i_{k,d_k}\}} \exp(\sum_j x_{ij} \beta_j)\}$ for the denominator of Cox's modification

$$pL(\beta) = \prod_{k=1}^K \frac{\prod_{i \in \{i_{k,1}, \dots, i_{k,d_k}\}} \exp(\sum_j x_{ij} \beta_j)}{\prod_{m=1}^{d_k} \{\sum_{\ell \in \mathcal{R}(t_k)} \exp(\sum_{j=1}^p x_{\ell j} \beta_j) - \frac{m-1}{d_k} \sum_{i \in \{i_{k,1}, \dots, i_{k,d_k}\}} \exp(\sum_j x_{ij} \beta_j)\}}$$

- Default tie-handling method by `survival::coxph`

Summary of handling ties

- With no ties, all approximation options give exactly the same results
- With only a few ties, all approximations yield pretty much the same results
- With many ties (relative to the number at risk), both of Breslow's and Efron's approximations yield coefficients β that are biased toward 0.
- Computing time of Cox's method is substantially longer than that of approximate methods. But it is not a big issue with today's hardwares.
- The Efron's approximation almost always works better than the Breslow's method, without consuming more time.

Revisit Ex. 5.3. Leukemia data (with tied event/failure times)

```
library(survival)
data = survival::leukemia
fit1 = coxph(Surv(time,status)~x, data = data)
fit2 = coxph(Surv(time,status)~x, data = data, ties = 'efron')
fit3 = coxph(Surv(time,status)~x, data = data, ties = 'breslow')
fit4 = coxph(Surv(time,status)~x, data = data, ties = 'exact')
c(coef(fit1), coef(fit2), coef(fit3), coef(fit4))
```

CIs and hypothesis tests for HRs

- Suppose the HR of interest is the one associated with the one-unit increase of the j th covariate, i.e., $\exp(\beta_j)$
- $\text{var}\{\exp(\hat{\beta}_j)\} \approx \exp(2\hat{\beta}_j) \text{var}(\hat{\beta}_j)$ (delta method)
 - Hence $\text{se}(\exp(\hat{\beta}_j)) \approx \exp(\hat{\beta}_j) \text{se}(\hat{\beta}_j)$
- 95% CI for $\exp(\beta_j)$
 - $\exp(\hat{\beta}_j) \pm \Phi^{-1}(.975) \times \text{se}(\exp(\hat{\beta}_j))$
 - * $\Phi^{-1}(.975) (\approx 1.96)$: the .975 quantile of $N(0, 1)$
 - $\exp(\hat{\beta}_j \pm \Phi^{-1}(.975) \times \text{se}(\hat{\beta}_j))$ (preferred; why?)
- Hypothesis test for $H_0 : \exp(\beta_j) = 1$ (i.e., $\beta_j = 0$) vs. H_1 : otherwise.
 - Wald test statistic: $\hat{\beta}_j / \text{se}(\hat{\beta}_j) \approx N(0, 1)$ under H_0
 - * Equivalent to checking whether $\exp(\hat{\beta}_j \pm \Phi^{-1}(.975) \times \text{se}(\hat{\beta}_j))$ covers 1
- LRT to compare two nested models

- Model 1 nested to Model 2
 - * Model 1: $\lambda(t | x_{i1}, \dots, x_{ip}) = \lambda_0(t) \exp(\sum_{j=1}^p x_{ij}\beta_j)$
 - * Model 2: $\lambda(t | x_{i1}, \dots, x_{ip}, x_{i,q+1}, \dots, x_{i,p+q}) = \lambda_0(t) \exp(\sum_{j=1}^{p+q} x_{ij}\beta_j)$
- H_0 : Model 1 is correct (i.e., $\beta_{p+1} = \dots = \beta_{p+q} = 0$) vs. H_1 : Model 2 is correct
- Test statistic: $2(\ln L_{\text{Model2}} - \ln L_{\text{Model1}}) \approx \chi^2(q)$ under H_0

Ex. 5.4. Nursing home data

- Variables:
 - ID: Patient ID
 - lstay: Length of stay of a resident (in days)
 - age: Age of a resident
 - trt: Nursing home assignment (1: receive treatment, 0: control)
 - gender: Gender (1:male, 0:female)
 - marstat: Marital status (1: married, 0: not married)
 - hlstat: Health status (2: second best, 5: worst)
 - cens: Censoring indicator (1:censored, 0: discharged)

```
options(digits=4)
library(survival)
data = read.csv("NursingHome.csv")
data$event <- 1-data$cens
head(data)
data$trt = factor(data$trt) # not necessary because it is of two levels
data$gender = factor(data$gender) # not necessary because it is of two levels
data$marstat = factor(data$marstat) # not necessary because it is of two levels
data$hlstat = factor(data$hlstat) # necessary because it is of more than two levels

fit1 <- coxph(Surv(lstay,event) ~ trt + age + gender + marstat + hlstat, data=data)
summary(fit1)

# Testing if trt is necessary against the full model
fit2 <- coxph(Surv(lstay,event) ~ age + gender + marstat + hlstat, data=data)
anova(fit1, fit2)
summary(fit2)

# Testing if trt, age and marstat are necessary against the full model
fit3 <- coxph(Surv(lstay,event) ~ gender + hlstat, data=data)
anova(fit1, fit3)
summary(fit3)
```

Estimating the baseline survival function

- Have to maximize the likelihood $L(\beta, \lambda_0)$ instead of the partial likelihood $pL(\beta)$
 - Assuming the cumulative baseline hazard $\Lambda_0(\cdot)$ as piecewise constant between failure times, Breslow (1972) proved that
 - * $L(\beta, \lambda_0)$ and $pL(\beta)$ share the identical maximizer, say $\hat{\beta}$, with respect to β
 - * The maximizer of $L(\beta, \lambda_0)$ with respect to λ_0 , say $\hat{\lambda}_0$, satisfies that

$$\hat{\Lambda}_0(t) = \sum_{k: t_k \leq t} \frac{d_k}{\sum_{\ell \in \mathcal{R}(t_k)} \exp(\sum_{j=1}^p x_{\ell j} \hat{\beta}_j)}$$

- $\hat{\Lambda}_0(t)$: Breslow estimator of the baseline cumulative hazard rate, reducing to the NA estimator (Lecture Note Part II) if all covariates are zeros

- d_k : # of events at t_k
- $\mathcal{R}(t_k)$: the risk set at t_k
- $\hat{S}_{T_i}(t) = \exp\{-\hat{\Lambda}_0(t)\}^{\exp(\sum_{j=1}^p x_{ij}\hat{\beta}_j)} = \hat{S}_0(t)^{\exp(\sum_{j=1}^p x_{ij}\hat{\beta}_j)}$
 – $\hat{S}_0(t) = \exp\{-\hat{\Lambda}_0(t)\}$: estimated baseline survival function

Ex. 5.4. Revisit the nursing home data

```
options(digits=4)
library(survival)
data.ex54 = read.csv("NursingHome.csv")
data.ex54$event <- 1-data.ex54$cens
data.ex54$marstat = factor(data.ex54$marstat) # not necessary because it is of two levels
data.ex54$hlstat = factor(data.ex54$hlstat) # necessary because it is of more than two levels
fit.ex54 <- coxph(Surv(lstay,event) ~ marstat + hlstat, data=data.ex54)
## P.S. note the mandatory scaling of covariates in `survival::coxph`

# baseline hazard and baseline survival
baseline <- basehaz(fit.ex54, centered = FALSE)
names(baseline)[1] = 'cum.haz'
baseline$surv = exp(-baseline$cum.haz)
baseline

# Plot the survival function with given values of covariates
newdata.ex54 <- data.frame(
  marstat = factor(c(0,0,1,1)),
  hlstat = factor(c(2,5,2,5))
)
newdata.ex54
cox.predicted.survival <- survfit(fit.ex54, newdata=newdata.ex54)
plot(
  cox.predicted.survival, lty=1:4, col=1:4, lwd=2,
  xlab="Survival Time", ylab="Estimated Survival Probability"
)
legend(
  "topright",
  c(
    "Not married, health status second best",
    "Not married, health status worst",
    "Married, health status second best",
    "Married, health status worst"
  ),
  lty=1:4, col=1:4, lwd=2
)
```