PH 716 Applied Survival Analysis
Part V: Cox Proportional Hazards Model

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Assumptions for Cox proportional hazards (PH) model

- Observed $\widetilde{T}_i = \tilde{t}_i$ and $\Delta_i = \delta_i$ (event indicator)

- T_i are independent across i, given $x_{i1}, \ldots, x_{ip}$

- The independent and non-informative censoring

- $\lambda_{T_i}(t) = \lambda(t \mid x_{i1}, \ldots, x_{ip}) = \lambda_0(t) \exp(\sum_{j=1}^{p} x_{ij}\beta_j)$, 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: nonparmetric baseline hazard + paramatric proportion
  - Proportional hazards: the HR between any two individuals, say $\lambda_{T_{i_1}}(t)/\lambda_{T_{i_2}}(t) = \exp(\sum_{j=1}^{p} x_{i_1 j}\beta_j - \sum_{j=1}^{p} x_{i_2 j}\beta_j)$, 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 jth 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 $\varepsilon_i \overset{\text{iid}}{\sim} F_{\varepsilon_i}(\epsilon) = 1 - \exp(-\exp \epsilon)$

  - $S_{T_i}(t) = \exp[-\{t/\exp(\beta_0 + \sum_{j=1}^{p} x_{ij}\beta_j)\}^{1/\sigma}] \Rightarrow \lambda_{T_i}(t) = (1/\sigma)t^{1/\sigma-1}\exp\{(-\beta_0 - \sum_{j=1}^{p} x_{ij}\beta_j)/\sigma\}$

- $\lambda_{T_i}(t) = \lambda_0(t)\exp(\sum_{j=1}^{p} x_{ij}\beta_j^*)$ if $\lambda_0(t) = (1/\sigma)t^{1/\sigma-1}\exp(-\beta_0/\sigma)$ and $\beta_j^* = -\beta_j/\sigma$, $j = 1, \ldots, p$

- 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 $L(\boldsymbol{\beta}, \lambda_0) = \prod_i \lambda_{T_i}(\tilde{t}_i)^{\delta_i} S_{T_i}(\tilde{t}_i)$ relying on both $\boldsymbol{\beta} = [\beta_1, \ldots, \beta_j]^\top$ and unspecified $\lambda_0(\cdot)$

- Further assumptions

  - K and only K distinct, ordered failure times, say $t_1 < \cdots < t_K$
  - 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 $\mathcal{R}(t) = \{i : \widetilde{T}_i \geq t\}$: the set of individuals who are known to survive just prior to time t

- Rephrase $L(\boldsymbol{\beta}, \lambda_0)$:

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

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

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

  as a surrogate of $L(\boldsymbol{\beta}, \lambda_0)$ in estimating $\boldsymbol{\beta}$

  - Cox (1972) argued that $pL(\boldsymbol{\beta})$ contained almost all the information about $\boldsymbol{\beta}$
  - 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

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

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

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

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 $t_1 < \cdots < t_K$
  - d_k failures at time t_k: there are d_k individuals, say subject $i_{k,1}, \ldots, i_{k,d_k}$, who fail at t_k
- Accordingly

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

  - $D(d_k) \subset \mathcal{R}(t_k)$: 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

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

- Default tie-handling method in SAS

Partial likelihood (Efron's approximation)

- Keeping the assumptions for the Cox's modification

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

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

- 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 $\boldsymbol{\beta}$ 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 jth covairate, i.e., $\exp(\beta_j)$

- $\mathrm{var}\{\exp(\hat{\beta}_j)\} \approx \exp(2\hat{\beta}_j)\mathrm{var}(\hat{\beta}_j)$ (delta method)

  - Hence $\mathrm{se}(\exp(\hat{\beta}_j)) \approx \exp(\hat{\beta}_j)\mathrm{se}(\hat{\beta}_j)$

- 95% CI for $\exp(\beta_j)$

  - $\exp(\hat{\beta}_j) \pm \Phi^{-1}(.975) \times \mathrm{se}(\exp(\hat{\beta}_j))$
    * $\Phi^{-1}(.975)$ (≈ 1.96): the .975 quantile of $N(0,1)$
  - $\exp(\hat{\beta}_j \pm \Phi^{-1}(.975) \times \mathrm{se}(\hat{\beta}_j))$ (preferred; why?)

- Hypothesis test for $H_0 : \exp(\beta_j) = 1$ (i.e., $\beta_j = 0$) vs. $H_1 :$ otherwise.

  - Wald test statistic: $\hat{\beta}_j/\mathrm{se}(\hat{\beta}_j) \approx N(0,1)$ under H_0
    * Equivalent to checking whether $\exp(\hat{\beta}_j \pm \Phi^{-1}(.975) \times \mathrm{se}(\hat{\beta}_j))$ covers 1

- LRT to compare two nested models

- Model 1 nested to Model 2
  * Model 1: $\lambda(t \mid x_{i1}, \ldots, x_{ip}) = \lambda_0(t) \exp(\sum_{j=1}^{p} x_{ij}\beta_j)$
  * Model 2: $\lambda(t \mid x_{i1}, \ldots, x_{ip}, x_{i,q+1}, \ldots, x_{i,p+q}) = \lambda_0(t) \exp(\sum_{j=1}^{p+q} x_{ij}\beta_j)$
- H_0 : Model 1 is correct (i.e., $\beta_{p+1} = \cdots = \beta_{p+q} = 0$) 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)

```r
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)
```

Baseline cummulative hazard and 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
- $\widehat{S}_{T_i}(t) = \exp\{-\hat{\Lambda}_0(t)\}^{\exp(\sum_{j=1}^{p} x_{ij}\hat{\beta}_j)} = \widehat{S}_0(t)^{\exp(\sum_{j=1}^{p} x_{ij}\hat{\beta}_j)}$
  - − $\widehat{S}_0(t) = \exp\{-\hat{\Lambda}_0(t)\}$: estimated baseline survival function

Ex. 5.4. Revisit the nursing home data

```r
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
)
```