Cox proportional hazard model

Extensions

Cox PH model

- Recall Cox PH model assumes
  $$h(t|\boldsymbol{Z}) = h_0(t)\exp(\boldsymbol{Z}^T\boldsymbol{\beta})$$
- The effect of a covariate on hazard is constant over time.
- We have shown how to check PH assumption using Schoenfeld residuals.
- What if proportional hazard assumption is not satisfied?
- Consider extensions of Cox PH model to allow non-proportionality.
  - Stratified PH model: stratify over categorical covariate to allow different baseline hazard at different strata.
  - Cox model with time-varying covariates: Including interactions between time and the covariates.

Stratified PH model

Example: suppose we have two covariates:

= 1 if treatment, Z =0, if control

W =1 if male, W =0, if female

Goal: to assess the effect of treatment while controlling for gender.

Stratified PH model

Cox PH model with both covariates

$$h(t|Z,W) = h_0(t)\exp(Z\beta_1 + W\beta_2)$$

- It implies that the hazard functions of 4 subgroups are proportional with

$$h(t|Z=0,W=0) = h_0(t)$$
$$h(t|Z=1,W=0) = \exp(\beta_1)\, h_0(t)$$
$$h(t|Z=0,W=1) = \exp(\beta_2)\, h_0(t)$$
$$h(t|Z=1,W=0) = \exp(\beta_1+\beta_2)\, h_0(t)$$

Stratified PH model

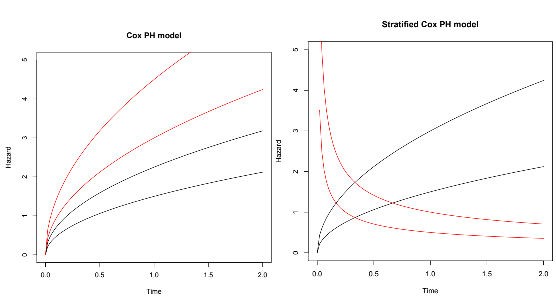
- Stratified PH model (by gender) assumes

$$h(t|Z=0,W=0) = h_0(t)$$
$$h(t|Z=0,W=1) = h_1(t)$$

- Strata specific baselines.
- For the effect of treatment, assume the same hazard ratio within each level W .

$$h(t|Z=1,W=0)=\exp(\beta)\, h_0(t)$$
$$h(t|Z=1,W=1)=\exp(\beta)\, h_1(t)$$

- Only PH assumption within stratum, not between stratums.



Stratified PH model

- If a categorical variable has K levels, the stratified PH model assumes
  $$h_k(t|Z)=h_{0k}(t)\exp(Z^T\beta).$$
- Each strata has its specific baseline $h_{0k}(t)$.
- Assume the effects of covariates Z is the same cross different stratums.
- The interpretation of covariate effect is similar as before. For example, for all stratums,
  $$\frac{h_k(t|Z=1)}{h_k(t|Z=0)}=\exp(\beta)$$

SAS Example

Treatment as a covariate
Gender as stratification variable

```
proc phreg;
baseline out = base survival = surv;
model time*censor(0  = treatment;
strata gender;
run;
```

Summary

- One way to deal with non-proportional covariates is stratified PH model.
- Stratification allows each stratum to have its own baseline hazard and solves the problem of non-proportionality of that variable.
- Drawbacks:
  - can not test the significance of the stratifying variable itself.
  - the number of parameters increase quickly with the number of stratums.
  - Only handles non-proportional for categorical variables

Time varying covariates

- Another way to deal with nonproportional covariates is to include interactions between time and the covariates.

$$h(t|Z) = h_0(t)\exp(Z\beta_1 + Zt\beta_2)$$

- It allows the effect of covariate Z to change over time.
- Essentially, we are creating a covariate that is time-varying.
- In practice, some covariates do change over the time.
  - Hourly blood pressure HIV patient CD4 counts
  - levels of air pollution

Time varying covariates

- Consider a Cox model with time-varying covariates

$$h(t|Z(t)) = h_0(t)\exp(Z(t)^T\beta)$$

- It is no longer proportional hazard since

$$\frac{h(t|Z(t))}{h_0(t)} = \exp(Z(t)^T\beta)$$

is no longer a constant over time.

SAS Example

Here is an example using covariate interactions with time as predictors to deal with non-proportionalilty of hazard.

```
proc phreg data=whas500;
class gender;
model lenfol*fstat(0) = gender age bmi|bmi hr
hrtime;
hrtime = hr*lenfol;
run;
```

Summary

Two extensions of Cox PH model
- Stratified Cox PH model
- Cox model with time-varying covariates