Lecture 7
Time-dependent Covariates in Cox Regression

So far, we've been considering the following Cox PH model:

$$\begin{aligned} \lambda(t|\mathbf{Z}) &= \lambda_0(t)\ \exp(\boldsymbol{\beta}'\mathbf{Z}) \\ &= \lambda_0(t) \exp(\textstyle\sum \beta_j Z_j) \end{aligned}$$

where β_j is the parameter for the the j-th covariate (Z_j).

Important features of this model:

(1) the baseline hazard depends on t, but not on the covariates $Z_1, ..., Z_p$

(2) the hazard ratio $\exp(\boldsymbol{\beta}'\mathbf{Z})$ depends on the covariates $Z_1, ..., Z_p$, but not on time t.

But there are cases where if we measure some of the Z_j's over time, they may vary. Eg. a patient's performance status, certain biomarkers, or –

Example to motivate time-dependent covariates

Stanford Heart transplant example:

Variables:

- SURVIVAL - time from program enrollment until death or censoring
- DEAD - indicator of death (1) or censoring (0)
- TRANSPL - whether patient ever had transplant
  (1 if yes, 2 if no)
- SURGERY - previous heart surgery prior to program
- AGE - age at time of acceptance into program
- WAIT - time from acceptance into program until transplant surgery (=. for those without transplant)

Initially, a Cox PH model was fit for predicting survival time:

$$\lambda(t|\mathbf{Z}) \;=\; \lambda_0(t)\;\exp(\beta_1 * transpl + \beta_2 * surgery + \beta_3 * age)$$

However, this model does not take into consideration that some patients had shorter waiting time to get transplants than others. A model with a time dependent indicator of whether a patient had a transplant at each point in time might be more appropriate.

Cox model with time-dependent covariates

$$\lambda(t|\mathbf{Z}(t)) = \lambda_0(t)\ \exp\{\boldsymbol{\beta}'\mathbf{Z}(t)\}$$

The hazard at time t depends (only) on the value of the covariates at that time, i.e $\mathbf{Z}(t)$. The regression effect of $\mathbf{Z}(\cdot)$ is constant $\boldsymbol{\beta}$ over time.

Some people do not call this model 'proportional hazards' any more, because the hazard ratio $\exp\{\boldsymbol{\beta}'\mathbf{Z}(t)\}$ varies over time. But many of us still use the term 'PH' loosely here.

Comparison with a single binary predictor (like heart transplant):

- A Cox PH model with time-independent covariate would compare the survival distributions between those without a transplant (ever) to those with a transplant. A subject's transplant status at the end of the study would determine which category they were put into for the entire study follow-up.
- A Cox model with time-dependent covariate would compare the risk of an event between transplant and non-transplant at each event time, but would re-evaluate which risk group each person belonged in based on whether they'd had a transplant by that time.

Inference:

We still use the **partial likelihood** to estimate $\boldsymbol{\beta}$

$$L(\boldsymbol{\beta}) = \prod_{i=1}^{n} \left[\frac{\exp\{\boldsymbol{\beta}' \mathbf{Z}_i(X_i)\}}{\Sigma_{j \in R(X_i)} \exp\{\boldsymbol{\beta}' \mathbf{Z}_j(X_i)\}} \right]^{\delta_i}$$

Note that each term in the partial likelihood is still the conditional probability of choosing individual i to fail from the risk set, given the risk set at time X_i and given that one failure is to occur.

Inference then proceeds similarly to the Cox model with time-independent covariates. The only difference is that the values of $\mathbf{Z}$ now changes at each risk set.

Example:
Suppose $Z(t)$ is a time-varying covariate:

				$Z(t)$						
ID	time	event	group	$t=3$	4	5	6	7	8	9
1	3	1	1	0						
6	4	0	0	1	1					
3	5	1	1	1	1	1				
2	5	0	1	0	0	0				
4	6	1	1	0	0	0	0			
7	7	1	0	0	0	0	1	1		
8	8	0	0	0	0	0	0	0	0	
5	8	0	1	0	0	0	0	1	1	
9	9	1	0	0	0	0	1	1	1	1
10	10	0	0	0	1	1	1	1	1	1

ordered failure time (τ_j)	Individuals at risk	failure ID	Partial Likelihood contribution
3			
5			
6			
7			
9			

(Be sure to do this exercise in order to be convinced that the procedure follows is valid for fitting the $Z(t)$ model.)

Results from fitting two models

Model with time-independent $Z(3)$:

Testing Global Null Hypothesis: BETA=0

Criterion	Without Covariates	With Covariates	Model Chi-Square
-2 LOG L	16.953	13.699	3.254 with 2 DF (p=0.1965)
Score	.	.	3.669 with 2 DF (p=0.1597)
Wald	.	.	2.927 with 2 DF (p=0.2315)

Analysis of Maximum Likelihood Estimates

Variable	DF	Parameter Estimate	Standard Error	Wald Chi-Square	Pr > Chi-Square	Risk Ratio
GROUP	1	1.610529	1.21521	1.75644	0.1851	5.005
Z2	1	1.360533	1.42009	0.91788	0.3380	3.898

Model with time-dependent $Z(t)$:

Testing Global Null Hypothesis: BETA=0

Criterion	Without Covariates	With Covariates	Model Chi-Square
-2 LOG L	16.953	14.226	2.727 with 2 DF (p=0.2558)
Score	.	.	2.725 with 2 DF (p=0.2560)
Wald	.	.	2.271 with 2 DF (p=0.3212)

Analysis of Maximum Likelihood Estimates

Variable	DF	Parameter Estimate	Standard Error	Wald Chi-Square	Pr > Chi-Square	Risk Ratio
GROUP	1	1.826757	1.22863	2.21066	0.1371	6.214
Z	1	0.705963	1.20630	0.34249	0.5584	2.026

Time-varying covariates in R (and most software)

The original data on page 4 may be stored as ('wide' format):

Table 1: A Toy Data Example

Subject ID	Group	Z1	Time1	Z2	Time2	Status
1	1	0	3			1
2	1	0	5			0
3	1	1	5			1
4	1	0	6			1
5	1	0	6	1	8	0
6	0	1	4			0
7	0	0	5	1	7	1
8	0	0	8			0
9	0	0	5	1	9	1
10	0	0	3	1	10	0

We first need to create a data set with start (or 'time') and stop ('time2') values of time ('long' format):

```
id start stop status group   z
 1     0    3      1     1   0
 2     0    5      0     1   0
 3     0    5      1     1   1
 4     0    6      1     1   0
 5     0    6      0     1   0
 5     6    8      0     1   1
 6     0    4      0     0   1
 7     0    5      0     0   0
 7     5    7      1     0   1
 8     0    8      0     0   0
 9     0    5      0     0   0
 9     5    9      1     0   1
10     0    3      0     0   0
10     3   10      0     0   1
```

Note that each different value of $Z(t)$ for a subject generates a row of pseudo data.

The R command to fit the Cox model would then be: 'coxph(Surv(time=start, time2=stop, status) ~ group + z, data)'.

Results:

```
 Alive Dead Deleted
     9    5       0

      coef exp(coef) se(coef)     z     p
[1,] 1.827      6.21     1.23 1.487 0.137
[2,] 0.706      2.03     1.21 0.585 0.558

     exp(coef) exp(-coef) lower .95 upper .95
[1,]      6.21      0.161     0.559      69.0
[2,]      2.03      0.494     0.190      21.5

Likelihood ratio test= 2.73  on 2 df,   p=0.256
Efficient score test = 2.73  on 2 df,   p=0.256
```

Q: why is this approach valid?
(hint: write down the likelihood)

Note: this form of Surv() is also used to handle left truncated data, where 'time' is the truncation (entry) time Q, and 'time2' is the event time.

Most other softwares handle time-dependent covariates similarly (Stata). SAS has multiple programming options (see Allison book).

Applications

The Cox model where time-dependent covariates is used:

I. When **important covariates change** during a study

- **Framingham Heart study**

  5209 subjects followed since 1948 to examine relationship between risk factors and cardiovascular disease. A particular example:

  Outcome: time to congestive heart failure
  Predictors: age, systolic blood pressure, # cigarettes per day

- **Liver Cirrhosis** (Andersen and Gill, p.528)

  Clinical trial comparing treatment to placebo for cirrhosis. The outcome of interest is time to death. Patients were seen at the clinic after 3, 6 and 12 months, then yearly.

  Fixed covariates: treatment, gender, age (at diagnosis)
  Time-varying covariates: alcohol consumption, nutritional status, bleeding, albumin, bilirubin, alkaline phosphatase and prothrombin.

- **Recidivism study:** (Allison 'Survival Analysis Using SAS', p.42)
  432 male inmates were followed for one year after release from prison, to evaluate risk of re-arrest as function of financial aid (FIN), age at release (AGE), race (RACE), full-time work experience prior to first arrest (WEXP), marital status (MAR), parole status (PARO=1 if released with parole, 0 otherwise), and number of prior convictions (PRIO). Data were also collected on employment status over time during the year.

  Time-independent model:
  A time independent model might include the employment status of the individual at the beginning of the study (1 if employed, 0 if unemployed), or perhaps at any point during the year.

  Time-dependent model:
  However, employment status changes over time, and it may be the more recent employment status that would affect the hazard for re-arrest. For example, we might want to define a time-dependent covariate for each month of the study that indicates whether the individual was employed during the past month.

Recidivism Example:

Hazard for arrest within one year of release from prison:

Model without employment status

Testing Global Null Hypothesis: BETA=0

Criterion	Without Covariates	With Covariates	Model Chi-Square
-2 LOG L	1350.751	1317.496	33.266 with 7 DF (p=0.0001)
Score	.	.	33.529 with 7 DF (p=0.0001)
Wald	.	.	32.113 with 7 DF (p=0.0001)

Analysis of Maximum Likelihood Estimates

Variable	DF	Parameter Estimate	Standard Error	Wald Chi-Square	Pr > Chi-Square	Risk Ratio
FIN	1	-0.379422	0.1914	3.931	0.0474	0.684
AGE	1	-0.057438	0.0220	6.817	0.0090	0.944
RACE	1	0.313900	0.3080	1.039	0.3081	1.369
WEXP	1	-0.149796	0.2122	0.498	0.4803	0.861
MAR	1	-0.433704	0.3819	1.290	0.2561	0.648
PARO	1	-0.084871	0.1958	0.188	0.6646	0.919
PRIO	1	0.091497	0.0287	10.200	0.0014	1.096

What are the important predictors of recidivism?

Recidivism Example: Output

Model WITH employment as time-dependent covariate

Analysis of Maximum Likelihood Estimates

Variable	DF	Parameter Estimate	Standard Error	Wald Chi-Square	Pr > Chi-Square	Risk Ratio
FIN	1	-0.356722	0.1911	3.484	0.0620	0.700
AGE	1	-0.046342	0.0217	4.545	0.0330	0.955
RACE	1	0.338658	0.3096	1.197	0.2740	1.403
WEXP	1	-0.025553	0.2114	0.015	0.9038	0.975
MAR	1	-0.293747	0.3830	0.488	0.4431	0.745
PARO	1	-0.064206	0.1947	0.109	0.7416	0.938
PRIO	1	0.085139	0.0290	8.644	0.0033	1.089
EMPLOYED	1	-1.328321	0.2507	28.070	0.0001	0.265

Is current employment important?

Do the other covariates change much?

Can you think of any problem with using current employment as a predictor?

Another option for assessing impact of employment

Allison suggests using the employment status of the past week rather than the current week.

The coefficient for EMPLOYED changes from -1.33 to -0.79, so the risk ratio is about 0.45 instead of 0.27. It is still highly significant with $\chi^2 = 13.1$.

Does this model improve the causal interpretation?

Other options for time-dependent covariates:

- multiple lags of employment status (week-1, week-2, etc.)
- cumulative employment experience (proportion of weeks worked)

II. For **cross-over studies**, to indicate change in treatment

- **Stanford heart study** (Cox and Oakes p.129)
  Between 1967 and 1980, 249 patients entered a program at Stanford University where they were registered to receive a heart transplant. Of these, 184 received transplants, 57 died while waiting, and 8 dropped out of the program for other reasons. Does getting a heart transplant improve survival? Here is a sample of the data:

Waiting time	transplant?	survival post transplant	total survival	final status
49	2	.	.	1
5	2	.	.	1
0	1	15	15	1
35	1	3	38	1
17	2	.	.	1
11	1	46	57	1

etc

(survival is not indicated above for those without transplants, but was available in the dataset)

Naive approach: Compare the total survival of transplanted and non-transplanted.

Problem: Selection (length) Bias (why?). In causal inference, the treatment assignment is wrong at t for those who received transplant after t. See also Xu et al. (2012).

RESULTS for Stanford Heart Transplant data:

Naive model with fixed transplant indicator:

Criterion	Covariates	Covariates	Model Chi-Square
-2 LOG L	718.896	674.699	44.198 with 1 DF (p=0.0001)
Score	.	.	68.194 with 1 DF (p=0.0001)
Wald	.	.	51.720 with 1 DF (p=0.0001)

Analysis of Maximum Likelihood Estimates

Variable	DF	Parameter Estimate	Standard Error	Wald Chi-Square	Pr > Chi-Square	Risk Ratio
TSTAT	1	-1.999356	0.27801	51.72039	0.0001	0.135

Model with time-dependent transplant indicator:

Testing Global Null Hypothesis: BETA=0

Criterion	Without Covariates	With Covariates	Model Chi-Square
-2 LOG L	1330.220	1312.710	17.510 with 1 DF (p=0.0001)
Score	.	.	17.740 with 1 DF (p=0.0001)
Wald	.	.	17.151 with 1 DF (p=0.0001)

Analysis of Maximum Likelihood Estimates

Variable	DF	Parameter Estimate	Standard Error	Wald Chi-Square	Pr > Chi-Square	Risk Ratio
TSTAT	1	-0.965605	0.23316	17.15084	0.0001	0.381

The second model took about twice as long to run as the first model, which is usually the case for models with time-dependent covariates.

III. For **testing the PH assumption**

For example, we can fit these two models:

(1) **Time independent covariate** Z_1

$$\lambda(t, \mathbf{Z}) \;=\; \lambda_0(t)\;\exp(\beta_1 * Z_1)$$

The hazard ratio for Z_1 is $\exp(\beta_1)$.

(2) **Time dependent covariate** Z_1

$$\lambda(t, \mathbf{Z}) \;=\; \lambda_0(t)\;\exp(\beta_1 * Z_1 + \beta_2 * Z_1 * t)$$

The hazard ratio for Z_1 is $\exp(\beta_1 + \beta_2 t)$.

A test of the parameter $\beta_2 = 0$ is a test of the PH assumption.

Q: what are the pros and cons of such a test?

(We will talk more about testing the PH assumption.)

Illustration: Colon Cancer data

Model without time*stage interaction

Event and Censored Values

Total	Event	Censored	Percent Censored
274	218	56	20.44

Testing Global Null Hypothesis: BETA=0

Criterion	Without Covariates	With Covariates	Model Chi-Square
-2 LOG L	1959.927	1939.654	20.273 with 2 DF (p=0.0001)
Score	.	.	18.762 with 2 DF (p=0.0001)
Wald	.	.	18.017 with 2 DF (p=0.0001)

Analysis of Maximum Likelihood Estimates

Variable	DF	Parameter Estimate	Standard Error	Wald Chi-Square	Pr > Chi-Square	Risk Ratio
TRTM	1	0.016675	0.13650	0.01492	0.9028	1.017
STAGEN	1	-0.701408	0.16539	17.98448	0.0001	0.496

Model WITH time*stage interaction

Testing Global Null Hypothesis: BETA=0

Criterion	Without Covariates	With Covariates	Model Chi-Square
-2 LOG L	1959.927	1902.374	57.553 with 3 DF (p=0.0001)
Score	.	.	35.960 with 3 DF (p=0.0001)
Wald	.	.	19.319 with 3 DF (p=0.0002)

Analysis of Maximum Likelihood Estimates

Variable	DF	Parameter Estimate	Standard Error	Wald Chi-Square	Pr > Chi-Square	Risk Ratio
TRTM	1	0.008309	0.13654	0.00370	0.9515	1.008
STAGEN	1	1.402244	0.45524	9.48774	0.0021	4.064
TSTAGE	1	-8.322371	2.04554	16.55310	0.0001	0.000

Notice the change in sign of stage effect alone?
The time-varying effect of stage is: $1.4 - 8.32t$, compared to the fixed effect of $\beta = -0.7$ from the first model.

Ex: think about how to fit the above interaction model?

Like in Cox and Oakes, we can run a few different models on covariates by time interaction, other than the linear effect of time.

IV. For **fitting non-PH models**

The second model in the above is a non-proportional hazards model.

In general, a **non-proportional hazards** model can be written

$$\lambda(t|\mathbf{Z}) = \lambda_0(t) \exp\{\boldsymbol{\beta}(t)'\mathbf{Z}\}$$

so that the regression effect of $\mathbf{Z}$ changes with time.

We can put different assumptions on $\boldsymbol{\beta}(t)$. We can model it as piecewise constant, linear (as in the previous example) or piecewise linear, or piecewise cubic (spline), etc.

Piecewise constant $\boldsymbol{\beta}(t)$:

- Depending on how we dividing the intervals, the piecewise constant model can approximate any shape of $\boldsymbol{\beta}(t)$.
- It is relatively easy to fit (see below).
- It has simple interpretations; eg. the hazard ratio is xxx from t_1 to t_2, etc.
- Without any other indications, we often take equal number of events per interval.

When $\boldsymbol{\beta}(t)$ is piecewise constant, the non-PH model can be written as a Cox model with time-dependent covariates, as in the following.

Suppose $0 = t_0 < t_1 < t_2 < ... < t_K$, and $\boldsymbol{\beta}(t) = \boldsymbol{\beta}_k$ on $[t_{k-1}, t_k)$, i.e.,

$$\boldsymbol{\beta}(t) = \sum_{k=1}^{K} \boldsymbol{\beta}_k I_{[t_{k-1},t_k)}(t)$$

where $I_{[t_{k-1},t_k)}(\cdot)$ is the indicator function for interval $[t_{k-1}, t_k)$.

Then

$$\begin{aligned} \boldsymbol{\beta}(t)'\mathbf{Z} &= \{\sum_{k=1}^{K} \boldsymbol{\beta}_k I_{[t_{k-1},t_k)}(t)\}'\mathbf{Z} \\ &= \sum_{k=1}^{K} \boldsymbol{\beta}_k'\{I_{[t_{k-1},t_k)}(t)\mathbf{Z}\} \\ &= \sum_{k=1}^{K} \boldsymbol{\beta}_k'\mathbf{Z}_k(t) \end{aligned}$$

where $\mathbf{Z}_k(t) = I_{[t_{k-1},t_k)}(t)\mathbf{Z}$.

One can show that fitting the above $\mathbf{Z}(t)$ using partial likelihood is in fact equivalent to: estimating $\boldsymbol{\beta}_k$ using the survival data in the interval $[t_{k-1}, t_k)$, by excluding all those data points i such that $X_i < t_{k-1}$, and treating all those i such that $X_i \geq t_k$ as censored (i.e. set $\delta_i = 0$ for estimating $\boldsymbol{\beta}_k$).

Exercise: prove the above for $K = 3$ using the partial likelihood. Can you make a connection here to left truncation, what do you learn?

There are ways to search for an optimal change point of $\beta(t)$; see O'Quigley and Pessione (1991).

There are also ways to find multiple change points using a tree-based approach, following which a piecewise constant $\beta(t)$ can be fitted; see Xu and Adak (2002).

Some further notes

In practice, $Z(t)$ may not be measured at each time point t. What do we do?

- use the most recent value (assumes step function)
- interpolate
- impute based on some model for the 'missing' mechanism

Types of time-varying covariates:

- **internal covariates:**

  variables that relate to the individuals, and can only be measured when an individual is alive, e.g. white blood cell count, CD4 count

- **external covariates:**
  - variable which changes in a known way, e.g. age, dose of drug
  - variable that exists totally independently of all individuals, e.g. air temperature

These concepts are relavent particularly when predicting survival (estimating $S(t|Z)$). It is difficult to predict survival based on internal covariates. Often survival prediction is done only based on time-independent covariates.

Some cautionary notes

- Time-varying covariates must be carefully constructed to ensure interpretability. (What is the interpretation of $\boldsymbol{\beta}$?)
- There is no point adding a time-varying covariate whose value changes the same as study time ..... you will get the same answer as using a fixed covariate measured at study entry. For example, suppose we want to study the effect of age on time to death.

  We could

  1. use age at start of the study as a fixed covariate
  2. age as a time varying covariate

  However, the results will be the same! Why?

Technical assumption:

$\mathbf{Z}(t)$ needs to be *predictable* (given the history up to $t-$) in order to apply the martingale theory to the Cox model.