Applied survival analysis

Constantin T Yiannoutsos, Ph.D.

January 24, 2016

Contents of today's lecture

1. **Time-dependent covariates**
   - Introduction
   - The Stanford heart-transplant data
   - Analysis of the Stanford heart transplant data
   - The counting process approach to survival analysis
   - R analysis of the Crowley & Hu data

2. **Checking the PH assumption via time-updated covariates**
   - Introduction
   - Re-analysis of the leukemia data set

Time-dependent covariates

In many situations it is useful to consider covariates that change over time. These are called “time-dependent” covariates. Such are of two kinds:

1. Internal variables
   These are related to each patient and are measurable while the patient is under observation
2. External variables
   These are variables that do not depend on the physical observation of the patient such as
   1. Variables such as age that are known once the birth date or age at enrollment to the study is known
   2. Variables that are independent of any individual like levels of pollution or temperature

Time-updated covariates and the Cox model

These time-updated or dependent variables can be entered into the Cox model in direct extension of the simpler non-time-updated case

$$\lambda_i(t;\mathbf{Z}_i) = \lambda_0(t)\exp\sum_{j=1}^{n}\beta_j Z_{ij}(t)$$

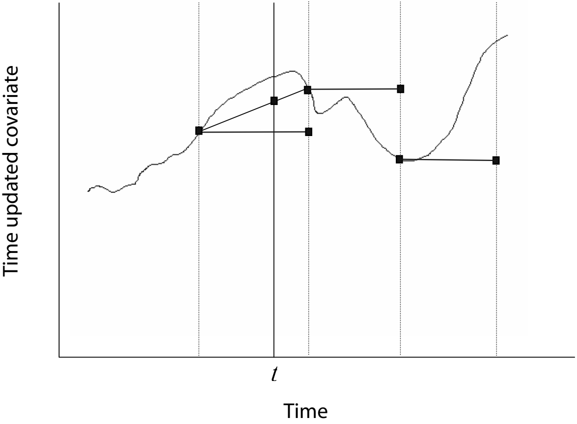
where $\lambda_0(t)$ is the baseline hazard associated with all covariates being equal to zero *during all time points* t. So the Cox model is generalized as

$$\sum_{i=1}^{n}\delta_i\left\{\sum_{j=1}^{p}\beta_j Z_{ij}(t_i) - \log\sum_{l\in R(t_i)}\exp\left(\sum_{j=1}^{p}\beta_j Z_{jl}(t_i)\right)\right\}$$

this means that we will need to have all the variable (especially internal ones) available at each event time. It is important to understand that this is no longer a proportional hazards model.

Imputing time-updated covariates

When the value of a time-updated covariate is not known during a failure time t we can use various methods to fill in a value for a particular time (see figure below). We can either extend the most recent value or, if two values are available on either side of the time point we can use interpolation.



The Stanford heart transplant data

We present here the famous Stanford heart transplant data set (Crowley & Hu, 1977). In this data set, 103 individuals waiting for a heart transplant were followed for survival. The problem that the study presented to the original investigators (and us) is that the effect of heart transplantation on survival is impossible to assess given the methods that we have been exposed to.

The reason is that the hazard of an individual is different before and after a transplantation and, for an individual to receive a transplant, they have to have survived up to the point that an organ is available. As Collett describes the situation (Section 7.3), the two groups are also not comparable at the time origin (entry into the study and time from transplantation).

Analysis via a conventional Cox PH model

Before considering the correct analysis, let's perform a naive analysis involving a conventional PH model

```
Call:
coxph(formula = Surv(time, fail) ~ transplant, data = stanford)

  n= 103, number of events= 75

              coef exp(coef) se(coef)     z Pr(>|z|)
transplant -1.3238    0.2661   0.2438 -5.43 5.63e-08 ***
---
Signif. codes:  0 *** 0.001 ** 0.01 * 0.05 . 0.1   1

           exp(coef) exp(-coef) lower .95 upper .95
transplant    0.2661      3.758     0.165    0.4291

Concordance= 0.668  (se = 0.026 )
Rsquare= 0.223   (max possible= 0.997 )
Likelihood ratio test= 25.96  on 1 df,   p=3.481e-07
Wald test            = 29.49  on 1 df,   p=5.627e-08
Score (logrank) test = 33.41  on 1 df,   p=7.463e-09
```

Comments

This analysis indicates that transplantation is associated with one quarter of the hazard compared to no transplantation.

Given the misgivings about the appropriateness of the comparison, the solution is to introduce a time-updated covariate $Z(t)$ so that

$$Z(t) = \begin{cases} 1, \text{if } t > T_0 \\ 0, \text{if } t \leq T_0 \end{cases}$$

where T_0 is the time of transplantation.

Crowley and Hu suggest that the hazard associated with this situation is

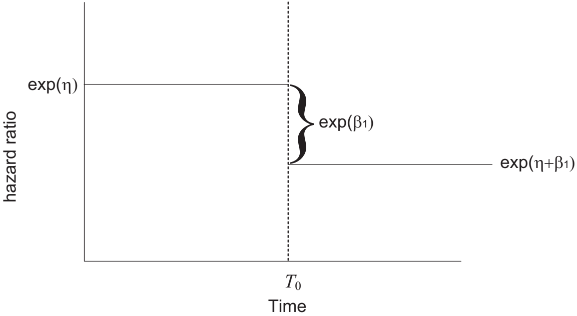
$$\lambda_i(t_i; \mathbf{Z}_i) = \lambda_0(t) \exp\{\eta_i + \beta_1 Z_{1i}(t)\}$$

where η_i is the summation of the products of all other covariates and their associated coefficients (excluding $Z_{1i}(t)$) measured on each individual i at each time t.

The hazard ratio (according to Crowley and Hu, 1977) is

$$\frac{\lambda(t_i;\mathbf{Z}_1(t))}{\lambda(t_i;\mathbf{Z}_0(t))} = \begin{cases} \exp\left\{\eta_i\right\}, \text{ before tranplantation} \\ \exp\left\{\eta_i+\beta_1\right\}, \text{ after tranplantation} \end{cases}$$

If $\beta_1 < 0$ then the hazard ratio of two individuals (one without a transplant and one with one) looks as follows (where T_0 is the time of transplantation:



Further comments

In the original analysis, the effect of transplantation on the hazard is assessed by testing the significance of the coefficient β_1.

The null hypothesis $H_0 : \beta_1 = 0$ suggests that there is no effect on survival resulting from transplantation. On the other hand, the alternative hypothesis $H_A : \beta_1 < 0$ suggests a beneficial effect of the transplantation, while the alternative $H_A : \beta_1 > 0$ suggests a detrimental effect (increase in hazard of death) conferred by transplantation.

Cox & Oakes' reanalysis of the heart transplant data

The previous model does not account for the fact that a heart tranplantation is a delicate and very dangerous operation. Thus, even if the hazard is ultimately reduced from the pre-transplant levels, a period of very high hazard is likely to follow the operation. Cox and Oakes (1984) improve on the analysis of Crowley and Hu by introducing factors β_2 and β_3 as follows:

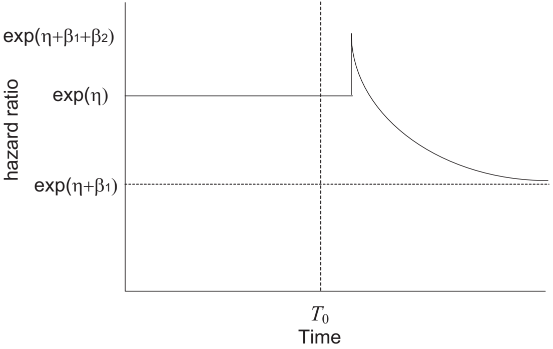
$$\lambda_i(t_i; \mathbf{Z}_i) = \lambda_0(t) \exp\left\{\eta_i + Z_{1i}(t)\left(\beta_1 + \beta_2 \exp[-\beta_3(t - T_0)]\right)\right\}$$

The hazard ratio is

$$\frac{\lambda(t_i; \mathbf{Z}_1(t))}{\lambda(t_i; \mathbf{Z}_0(t))} = \begin{cases} \exp\{\eta_i\}\text{, before tranplantation} \\ \exp\{\eta_i + \beta_1 + \beta_2\}\text{, right at tranplantation} \\ \exp\{\eta_i + \beta_1\}\text{, asymptotically (i.e., at } t \to \infty) \end{cases}$$

Graphical representation of the Cox & Oakes re-analysis

The Cox & Oakes reanalysis results in a hazard ratio that looks graphically as follows:



Notes

- In the reanalysis of Cox & Oakes, the effect of transplantation on the hazard is assessed by a more complex procedure.
- A large positive β_3 suggests a steep decrease of the hazard from an original level, just after transplantation, of $\exp(\eta_i + \beta_1 + \beta_2)$ to a level $\exp(\eta_i + \beta_1)$. A large positive value of β_2 suggests a large temporary increase of the hazard ratio post-transplantation. Conversely a smaller value of β_2 suggests small or negligible such increases.
- The latter asymptote ($\exp(\eta_i + \beta_1)$) depends on the magnitude and sign of β_1. The previous comments apply. That is, a large negative β_1 suggests a significant survival decrease (eventually) post tranplantation.
- Note that the Cox & Oakes model is equivalent to the Crowley & Hu model if $\beta_2 = 0$. The disadvantage of this model is that it requires specialized software to fit it.

Nuts and bolts

To perform any analysis involving the time-updated transplant status, we need to create two lines (one pre-transplantation and one post-transplantation) for the patients that received a transplant. Thus, the line for patient 95 for example in the original data set is

```
patid  year  age  fail  survtime  priorsurg  transplant  waitime  missallele  missantigen  misscore

  95    73    40    1       16        0           1          2         0            0         0.00
```

where waitime is the waiting time to transplantation. The data for this patient will be recoded as follows:

```
patid  year  age  fail  survtime  priorsurg  transplant  waitime  missallele  missantigen  misscore

  95    73    40    0        2        0           0          2         0            0         0.00
  95    73    40    1       16        0           1          2         0            0         0.00
```

in other words, we introduce a first (pre-transplantation) line with time going from $[0, 2)$ (i.e., just prior to transplantation.

Nuts and bolts (continued)

During that time $\delta_i = 0$ since no failure has occurred, and $Z_1(t) = 0$ since a transplantation has not taken place. The second line (post-transplantation) is associated with the time interval $[2, 16)$ i.e, the 14 months of post-transplantation survival. During that time δ_i is set to whatever the failure status of the patient is (in this case the patient died under observation, so $\delta_i = 1$. Also $Z_i(t) = 1$ here.

A situation arises with patient 38, who died on the same day of the transplantation (so waitime=survtime).

```
   patid transplant waitime  time fail
12    12          0      NA   8.0    1
16    16          1      20  43.0    1
38    38          1       5   5.1    1
80    80          1      26 482.0    0
```

Since this would cause most statistical software to exclude this case from consideration, we add a small fraction to the survival time (i.e., we assume that the patient lived a short time after receiving transplantation). This patient's data will look as follows:

```
     patid transplant waitime  time fail ord
12      12          0      NA   8.0    1   1
16      16          1      20  43.0    1   1
16.1    16          1      20  43.0    1   2
38      38          1       5   5.1    1   1
38.1    38          1       5   5.1    1   2
80      80          1      26 482.0    0   1
80.1    80          1      26 482.0    0   2
```

The counting process approach to survival analysis

A general approach to survival analysis was introduced by Andersen & Gill (1982) where each subject is considered as a counting process (counting events).

- $N_i(t)$ is the total number of events for each subject i up to time t
- $Y_i(t)$ is an indicator function with $Y_i(t) = 1$ if subject i is at risk at time t for the event

In this formulation the hazard is considered as an “intensity” process such that

$$\lambda_i(t) = Y_i(t)\lambda_0(t)\exp\{\beta' Z_i\}$$

Application of the counting process approach

By judicious choice of the various components of the process as defined above, the counting process approach can handle all kinds of survival data including

- Time updated covariates $Z_i(t)$
- Discontinuous risk sets
- Multiple events of the same or different type
  Here we replace $N_i(t)$, $Y_i(t)$ and $\lambda_0(t)$ by $N_i^{(k)}(t)$, $Y_i^{(k)}(t)$ and $\lambda_0^{(k)}(t)$ respectively for each event of type k (we will see more of that in a future lecture). By doing so, we can handle
  - Multiple failures of the different type (competing risks)
  - Multiple failures of the same type (both ordered and unordered)

R manipulation of the data

We begin by defining a starting (`tstart`) and stopping time (`tstop`) for each line of data for each patient:

```
     patid year age fail  time surgery transplant waitime ord tstop tstart
12      12   68  53    1   8.0       0          0      NA   1   8.0      0
16      16   68  56    0  43.0       0          0      20   1  20.0      0
16.1    16   68  56    1  43.0       0          1      20   2  43.0     20
38      38   70  41    0   5.1       0          0       5   1   5.0      0
38.1    38   70  41    1   5.1       0          1       5   2   5.1      5
80      80   72  46    0 482.0       1          0      26   1  26.0      0
80.1    80   72  46    0 482.0       1          1      26   2 482.0     26
```

Notice that the starting time in the first line for each patient (including those without transplant) is zero.

For those with a transplant (and, thus, having a second line of data) the ending time of the first interval is `waitime` and the starting time of the interval is the end of the previous interval (identical to `waitime`).

R analysis of the Crowley & Hu data

The R analysis of the Crowley & Hu model with only transplantation as the covariate is as follows (notice the new syntax within the Surv command):

```
Call:
coxph(formula = Surv(tstart, tstop, fail) ~ transplant, data = stanford2)

  n= 172, number of events= 75

             coef exp(coef) se(coef)     z Pr(>|z|)
transplant 0.1067    1.1126   0.2984 0.357    0.721

           exp(coef) exp(-coef) lower .95 upper .95
transplant     1.113     0.8988    0.6199     1.997

Concordance= 0.509  (se = 0.025 )
Rsquare= 0.001   (max possible= 0.969 )
Likelihood ratio test= 0.13  on 1 df,   p=0.7198
Wald test            = 0.13  on 1 df,   p=0.7207
Score (logrank) test = 0.13  on 1 df,   p=0.7207
```

Comments

The estimate of β_1 is $\hat{\beta}_1 = 0.1067$ associated with a hazard ratio of $e^{\beta_1} = 1.113$.

The interpretation is that transplantation increases slightly the hazard for death (by about 11%), an increase that is not statistically significant (p=0.720).

The log hazard ratio represented by β_1 concerns the comparison between a person that has undergone transplantation and one that has not.

Checking the PH assumption via time-updated covariates

As noted earlier, we can check the PH assumption by introducing an interaction between the effect and time

$$\lambda(t; Z) = \lambda_0(t)\ \exp\{\beta_1 Z_1 + \cdots + \beta_p Z_p + \gamma Z_1 * t\}$$

... or carrying out a stratified analysis

$$\lambda(t; Z) = \lambda_{0,Z_1}(t)\ \exp\{\beta_2 Z_2 + \cdots + \beta_p Z_p\}$$

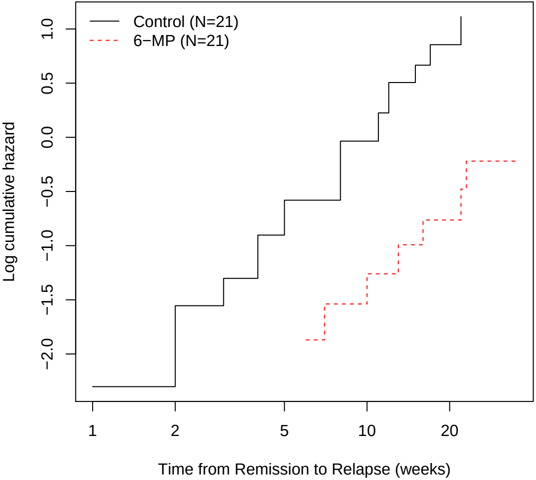
where $\lambda_{0,Z_i}(t)$ are baseline hazards over all levels of Z_1.

Notice that these are different analyses: In the first case we impose a *linear* change (increase or decrease depending on the sign of γ) on the hazard ratio over time, while, in the second case, the change of the baseline hazard over time in the various levels of Z_1 can be arbitrary.

We will focus here on the first case.

Re-analysis of the leukemia data set

Consider the check on the proportionality assumption in the case of the leukemia data:



Analysis by introduction of a treatment-time interaction

Even though the PH assumption appears to be fulfilled in this case, we will analyze the data by introducing a time-treatment interaction:

```
Call:
coxph(formula = Surv(weeks, remiss) ~ trt + I(weeks * (trt ==
    "6-MP")), data = leukem)

  n= 42, number of events= 30

                               coef exp(coef) se(coef)      z Pr(>|z|)
trtControl                 -1.47927   0.22780  0.81291 -1.820 0.068800 .
I(weeks * (trt == "6-MP")) -0.18138   0.83412  0.05479 -3.311 0.000931 ***
---
Signif. codes:  0 *** 0.001 ** 0.01 * 0.05 . 0.1   1

                           exp(coef) exp(-coef) lower .95 upper .95
trtControl                    0.2278      4.390    0.0463    1.1207
I(weeks * (trt == "6-MP"))    0.8341      1.199    0.7492    0.9287

Concordance= 0.773  (se = 0.06 )
Rsquare= 0.534   (max possible= 0.988 )
Likelihood ratio test= 32.11  on 2 df,   p=1.066e-07
Wald test            = 15.19  on 2 df,   p=0.0005029
Score (logrank) test = 25.11  on 2 df,   p=3.532e-06
```

Comments

Here we have $\gamma = -0.18138$, which is statistically significant. The interpretation is that the hazard ratio is *decreasing* linearly over time (in favor of 6-MP).

This is a surprising result given the previous figure, particularly given how strong this deviation from proportionality appears to be. (An almost 17% reduction in the hazard ratio *at each unit in time* above and beyond the overall four-fold reduction experienced by individuals treated with 6-MP).

In turn, this means that treatment with 6-MP has an accumulating benefit to the patient which increases over time.

Unfortunately, this is wrong!

Why was this the wrong analysis?

The previous model was wrong for the following reason: It inserted as a covariate for time the entire follow-up time for each patient!

So, even for risk sets involving failure times $\tau_j < T_i$, for the other subjects with $T_j < T_i$, the model, as structured, inserts the entire T_i as a covariate.

The correct analysis involves breaking up each T_i into each τ_j up to T_i and carrying out a time-updated analysis, similar to the one in the Crowley & Hu dataset, with `tstart` each failure time τ_j and `tstop` the next ranked failure time $\tau_{j'}$ up to T_i.

In R, this is done by the `tt` function. In Stata, this is done by the `tvc` option.

Note that this will increase the computational burden significantly in large data sets as it will add as many lines of data *for each patient* as there are failure times less than T_i[1].

[1] In fact, Stata recommends doing this manually when the `tvc` option fails in very large datasets using the `stsplit` command to create the additional data lines.

Correct analysis

The correct analysis is as follows:

```
Call:
coxph(formula = Surv(weeks, remiss) ~ trt + tt(trt), data = leukem,
    tt = function(x, t, ...) {
        x * t
    })

  n= 42, number of events= 30

              coef  exp(coef)   se(coef)      z Pr(>|z|)
trt     -1.5813338  0.2057005  0.7758258 -2.038   0.0415 *
tt(trt)  0.0008651  1.0008655  0.0616960  0.014   0.9888
---
Signif. codes:  0 *** 0.001 ** 0.01 * 0.05 . 0.1   1

        exp(coef) exp(-coef) lower .95 upper .95
trt        0.2057     4.8614   0.04496    0.9411
tt(trt)    1.0009     0.9991   0.88687    1.1295

Concordance= 0.69  (se = 0.188 )
Rsquare= 0.322   (max possible= 0.988 )
Likelihood ratio test= 16.35  on 2 df,   p=0.0002813
Wald test            = 14.51  on 2 df,   p=0.0007053
Score (logrank) test = 17.69  on 2 df,   p=0.0001443
```

Final comments

The above analysis shows that the estimate $\hat{\gamma} \approx 0$ (and not statistically significant).

This affirms the good fit of the Cox proportional hazards model for the leukemia data. It does not appear that there is any significant deviation from proportionality (at least in a linear fashion over time).

The above underlines the care that one must give to such analyses involving time as a covariate in the model.