Extensions to the Cox Model: Time Dependent Covariates

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Bone Marrow Transplant Data

- Copelan et al. (1991) study of allogenic bone marrow transplant therapy for acute myeloid leukemia (AML) and acute lymphoblastic leukemia (ALL).
- Possible intermediate events are graft vs. host disease (GVHD), an immunological rejection response to the transplant, and platelet recovery, a return of platelet count to normal levels. One or the other, both in either order, or neither may occur.
- End point events are relapse of the disease or death.
- Any or all of these events may be censored.

KMsurv bmt data

```
The bmt data frame has 137 rows and 22 columns.

This data frame contains the following columns:

group   Disease Group 1-ALL, 2-AML Low Risk, 3-AML High Risk
t1      Time To Death Or On Study Time
t2      Disease Free Survival Time (Time To Relapse, Death Or End Of Study)
d1      Death Indicator 1-Dead 0-Alive
d2      Relapse Indicator 1-Relapsed, 0-Disease Free
d3      Disease Free Survival Indicator 1-Dead Or Relapsed, 0-Alive Disease Free)
ta      Time To Acute Graft-Versus-Host Disease
da      Acute GVHD Indicator 1-Developed Acute GVHD 0-Never Developed Acute GVHD)
tc      Time To Chronic Graft-Versus-Host Disease
dc      Chronic GVHD Indicator 1-Developed Chronic GVHD
          0-Never Developed Chronic GVHD
tp      Time To Platelet Recovery
dp      Platelet Recovery Indicator 1-Platelets Returned To Normal,
          0-Platelets Never Returned to Normal
```

KMsurv bmt data

```
z1      Patient Age In Years
z2      Donor Age In Years
z3      Patient Sex: 1-Male, 0-Female
z4      Donor Sex: 1-Male, 0-Female
z5      Patient CMV Status: 1-CMV Positive, 0-CMV Negative
z6      Donor CMV Status: 1-CMV Positive, 0-CMV Negative
z7      Waiting Time to Transplant In Days
z8      FAB: 1-FAB Grade 4 Or 5 and AML, 0-Otherwise
z9      Hospital: 1-The Ohio State University, 2-Alferd , 3-St. Vincent,
          4-Hahnemann
z10     MTX Used as a Graft-Versus-Host- Prophylactic: 1-Yes 0-No
```

Bone Marrow Transplant Example

- The main endpoint is disease-free survival (t2 and d3) for the three risk groups, ALL, AML Low Risk, and AML High Risk.
- We are also interested in possibly using the covariates z1–z10 to adjust for other factors. We can do this with stepwise regression or hand examination of the results of adding or removing variables.
- In addition, the time-varying covariates for acute GVHD, chronic GVHD, and platelet recovery may be useful.

Time-Dependent Covariates

- A *time-dependent covariate* is one that changes value in the course of the study.
- For variables like age that change in a linear manner with time, we can just use the value at the start.
- But it may be plausible that when and if GVHD occurs, the risk of relapse or death increases, and when and if platelet recovery occurs, the risk decreases.

Formulation in R

- We form a variable `precovery` which is $= 0$ before platelet recovery and is $= 1$ after platelet recovery, if it occurs.
- For each subject where platelet recovery occurs, we set up multiple records (lines in the data frame); for example one from t $= 0$ to the time of platelet recovery, and one from that time to relapse, recovery, or death.
- We do the same for acute GVHD and chronic GVHD.
- For each record, the covariates are constant.

```
id group   t1   t2 d1 d2 d3 ta da  tc dc tp dp
 1   ALL 2081 2081  0  0  0 67  1 121  1 13  1


times are

t  = 0     time of transplant
tp = 13    platelet recovery
ta = 67    acute GVHD onset
tc = 121   chronic GVHD onset
t2 = 2081  end of study, patient not relapsed or dead

id group   tstart tstop agvhd cgvhd precovery status
 1   ALL       0    13     0     0         0      0
 1   ALL      13    67     0     0         1      0
 1   ALL      67   121     1     0         1      0
 1   ALL     121  2081     1     1         1      0  #this status could be 1
```

- Let A, C, and P stand for the event occurs for that patient at some time. Each of the eight possible combinations of A or not-A, with C or not-C, with P or not-P occurs in this data set.
- A always occurs before C and P always occurs before C if both occur.
- Thus there are ten kinds of patients in the data set: None, A, C, P, AC, AP, PA, PC, APC, and PAC.
- There could be as many as $1 + 3 + (3)(2) + 6 = 16$
- This is why a package to assist with this is helpful

- Different subjects could have 1, 2, 3, or 4 intervals depending on which of acute GVHD, chronic GVHD, and/or platelet recovery occurred.
- The final interval for any subject has status $= 1$ if the subject relapsed or died at that time, otherwise the status is 0.
- Any earlier intervals have status $= 0$.
- Even though there might be multiple lines in the data frame, there is never more than one event, so no alterations need be made in the estimation procedures or in the interpretation of the output.
- The function `tmerge` in the `survival package` eases the process of constructing the new data frame.

Fixed Covariates for the bmt Data

```
require(KMsurv)
require(survival)
data(bmt)
nsubj <- dim(bmt)[1]
id <- 1:nsubj
bmt1 <- data.frame(id,bmt)
bmt1$group <- factor(bmt1$group,labels=c("ALL","AML-Low","AML-High"))
bmt1$z9 <- factor(bmt1$z9) #hospital factor
bmt1.surv <- with(bmt1,Surv(t2,d3))

> drop1(coxph(bmt1.surv~group+z1*z2+z8+z9,data=bmt1),test="Chisq")
Single term deletions

Model:
bmt1.surv ~ group + z1 * z2 + z8 + z9
       Df    AIC     LRT  Pr(>Chi)
<none>    719.58
group   2 721.76  6.1738 0.0456426 *       #ALL, AML-High, AML-Low
z8      1 726.43  8.8504 0.0029303 **      #1-FAB Grade 4 Or 5 and AML, 0-Else
z9      3 725.79 12.2066 0.0067079 **      #Hospital
z1:z2   1 729.23 11.6537 0.0006407 ***     #Patient Age by Donor Age interaction
```

```
> summary(coxph(bmt1.surv~group+z1*z2+z8+z9,data=bmt1))
Call:
coxph(formula = bmt1.surv ~ group + z1 * z2 + z8 + z9, data = bmt1)

  n= 137, number of events= 83

                   coef  exp(coef)   se(coef)      z Pr(>|z|)
groupAML-Low  -0.7759558  0.4602636  0.3635689 -2.134 0.032820 *
groupAML-High -0.2379396  0.7882503  0.3577568 -0.665 0.505995
z1            -0.0982054  0.9064627  0.0378372 -2.595 0.009446 **
z2            -0.0823307  0.9209674  0.0301442 -2.731 0.006310 **
z8             0.8341968  2.3029635  0.2822471  2.956 0.003121 **
z92            0.7772511  2.1754838  0.3393736  2.290 0.022007 *
z93           -0.2766900  0.7582896  0.3365979 -0.822 0.411066
z94           -0.8881221  0.4114276  0.4204024 -2.113 0.034639 *
z1:z2          0.0035154  1.0035216  0.0009591  3.665 0.000247 ***
```

We will use the two age variables and FAP score in the following.
We omit the hospital effect since the significance test is possibly invalid (hospital-level effect, not patient effect).

```
bmt2 <- tmerge(bmt1,bmt1,id=id,tstop=t2)           #sets up new data set
bmt2 <- tmerge(bmt2,bmt1,id=id,agvhd=tdc(ta))      #adds afhvd as tdc
bmt2 <- tmerge(bmt2,bmt1,id=id,cgvhd=tdc(tc))      #adds cghvd as tdc
bmt2 <- tmerge(bmt2,bmt1,id=id,precovery=tdc(tp)) #adds platelet recovery as tdc

status <- as.integer(with(bmt2,(tstop==t2 & d3)))

# status only = 1 if at end of t2 and not censored

bmt2 <- data.frame(bmt2,status)

bmt2.surv <- with(bmt2,Surv(time=tstart,time2=tstop,event=status,type="counting"))

#counting process formulation of Surv
```

Add Time-Dependent Covariates

```
> summary(coxph(bmt2.surv~group+z1*z2+z8+agvhd+cgvhd+precovery,data=bmt2))

  n= 341, number of events= 83

                    coef  exp(coef)   se(coef)      z Pr(>|z|)
groupAML-Low  -1.0385144  0.3539802  0.3582204 -2.899  0.00374 **
groupAML-High -0.3804809  0.6835326  0.3748670 -1.015  0.31012
z1            -0.0733511  0.9292745  0.0359557 -2.040  0.04135 *
z2            -0.0764062  0.9264398  0.0301965 -2.530  0.01140 *
z8             0.8057002  2.2382632  0.2842726  2.834  0.00459 **
agvhd          0.1505649  1.1624908  0.3068484  0.491  0.62365
cgvhd         -0.1161359  0.8903542  0.2890463 -0.402  0.68784
precovery     -0.9411227  0.3901895  0.3478611 -2.705  0.00682 **
z1:z2          0.0028946  1.0028988  0.0009435  3.068  0.00216 **
```

Neither acute GVHD nor chronic GVHD has a statistically significant effect here or in a model with the other one removed. Platelet recovery is highly significant.

```
> summary(coxph(bmt2.surv~group+z1*z2+z8+precovery,data=bmt2))

  n= 341, number of events= 83

                    coef  exp(coef)   se(coef)      z Pr(>|z|)
groupAML-Low  -1.0325200  0.3561084  0.3532019 -2.923  0.00346 **
groupAML-High -0.4138881  0.6610749  0.3652095 -1.133  0.25709
z1            -0.0709647  0.9314948  0.0354533 -2.002  0.04532 *
z2            -0.0760524  0.9267677  0.0300071 -2.534  0.01126 *
z8             0.8119262  2.2522421  0.2832310  2.867  0.00415 **
precovery     -0.9835053  0.3739978  0.3379970 -2.910  0.00362 **
z1:z2          0.0028716  1.0028758  0.0009355  3.070  0.00214 **
---
Signif. codes:  0 *** 0.001 ** 0.01 * 0.05 . 0.1   1

              exp(coef) exp(-coef) lower .95 upper .95
groupAML-Low     0.3561     2.8081    0.1782    0.7116
groupAML-High    0.6611     1.5127    0.3231    1.3524
z1               0.9315     1.0735    0.8690    0.9985
z2               0.9268     1.0790    0.8738    0.9829
z8               2.2522     0.4440    1.2928    3.9238
precovery        0.3740     2.6738    0.1928    0.7254
z1:z2            1.0029     0.9971    1.0010    1.0047
```

Recurrent Events

- Sometimes an appropriate analysis requires consideration of recurrent events.
- A patient with arthritis may have more than one flareup. The same is true of many recurring-remitting diseases.
- In this case, we have more than one line in the dataframe, but each line may have an event.
- We have to use a "robust" variance estimator to account for correlation of time-to-events within a patient.

Bladder Cancer Data Set

The bladder cancer dataset from Kleinbaum and Klein contains recurrent event outcome information for eighty-six cancer patients followed for the recurrence of bladder cancer tumor after transurethral surgical excision (Byar and Green 1980). The exposure of interest is the effect of the drug treatment of thiotepa. Control variables are the initial number and initial size of tumors. The data layout is suitable for a counting processes approach.
This drug is still a possible choice for some patients. Another therapeutic choice is Bacillus Calmette-Guerin (BCG), a live bacterium related to cow tuberculosis.

Bladder Cancer Data Set

Variable	Definition
id	Patient unique ID
status	for each time interval
	1 = recurred
	2 = censored
interval	1 = first recurrence, etc.
intime	tstop − tstart
tstart	start of interval
tstop	end of interval
tx	treatment code, 1 = thiotepa
num	number of initial tumors
size	size of initial tumors (cm)

- There are 85 patients and 190 lines in the dataframe, meaning that many patients have more than one line.
- Patient 1 with 0 observation time was removed.
- Of the 85 patients, 47 had at least one recurrence and 38 had none.
- 18 patients had exactly one recurrence.
- There were up to 4 recurrences in a patient.
- Of the 190 intervals, 112 terminated with a recurrence and 78 were censored.

- Different intervals for the same patient are correlated.
- Of the 85 patients, 47 had at least one recurrence and 38 had none.
- Of the 190 intervals, 112 terminated with a recurrence and 78 were censored.
- Is the effective sample size 47 or 112? This might narrow confidence intervals by as much as a factor of $\sqrt{112/47} = 1.54$
- What happens if I have 5 treatment and 5 control values and want to do a t-test and I then duplicate the 10 values as if the sample size was 20? This falsely narrows confidence intervals by a factor of $\sqrt{2} = 1.41$.

```
require(survival)
vars <- c("id","status","interval","intime","tstart","tstop","tx","num","size")
bladder <- read.table("bladder.dat",header=F,col.names=vars)
bladder <- bladder[-1,]  #remove subject with 0 observation time

#bladder.dat from Kleinbaum and Klein with lines before and after data removed

bladder.surv <- with(bladder,Surv(time=tstart,time2=tstop,event=status,
                    type="counting"))

bladder.cox1 <- coxph(bladder.surv~tx+num+size,data=bladder)
#biased variance co-variance matrix

bladder.cox2 <- coxph(bladder.surv~tx+num+size+cluster(id),data=bladder)
#unbiased though this reduces power

bladder.cox3 <- coxph(bladder.surv~tx+num+cluster(id),data=bladder)
#remove non-significant size variable
```

```
> summary(bladder.cox1)
Call:
coxph(formula = bladder.surv ~ tx + num + size, data = bladder)

  n= 190, number of events= 112

         coef exp(coef) se(coef)      z Pr(>|z|)
tx   -0.41164   0.66256  0.19989 -2.059 0.039466 *
num   0.16367   1.17782  0.04777  3.426 0.000611 ***
size -0.04108   0.95975  0.07029 -0.584 0.558967

> summary(bladder.cox2)
Call:
coxph(formula = bladder.surv ~ tx + num + size + cluster(id),
    data = bladder)

  n= 190, number of events= 112

         coef exp(coef) se(coef) robust se      z Pr(>|z|)
tx   -0.41164   0.66256  0.19989   0.24876 -1.655  0.09798 .
num   0.16367   1.17782  0.04777   0.05842  2.801  0.00509 **
size -0.04108   0.95975  0.07029   0.07421 -0.554  0.57991
```

```
> summary(bladder.cox1)
     exp(coef) exp(-coef) lower .95 upper .95
tx      0.6626      1.509    0.4478    0.9803
num     1.1778      0.849    1.0726    1.2934
size    0.9598      1.042    0.8362    1.1015
```

```
> summary(bladder.cox2)
     exp(coef) exp(-coef) lower .95 upper .95
tx      0.6626      1.509    0.4069     1.079
num     1.1778      0.849    1.0504     1.321
size    0.9598      1.042    0.8298     1.110
```

```
> summary(bladder.cox1)

Concordance= 0.624  (se = 0.03 )
Rsquare= 0.074   (max possible= 0.992 )
Likelihood ratio test= 14.66  on 3 df,   p=0.002127
Wald test            = 15.9  on 3 df,   p=0.001187
Score (logrank) test = 16.18  on 3 df,   p=0.001042

> summary(bladder.cox2)

Concordance= 0.624  (se = 0.03 )
Rsquare= 0.074   (max possible= 0.992 )
Likelihood ratio test= 14.66  on 3 df,   p=0.002127
Wald test            = 11.19  on 3 df,   p=0.01073
Score (logrank) test = 16.18  on 3 df,   p=0.001042,   Robust = 10.84  p=0.01263

  (Note: the likelihood ratio and score tests assume independence of
     observations within a cluster, the Wald and robust score tests do not).
```

```
> round(bladder.cox2$naive.var,4)
        [,1]    [,2]   [,3]
[1,]  0.0400 -0.0014 0.0000
[2,] -0.0014  0.0023 0.0007
[3,]  0.0000  0.0007 0.0049

> round(bladder.cox2$var,4)
        [,1]    [,2]    [,3]
[1,]  0.0619 -0.0026 -0.0004
[2,] -0.0026  0.0034  0.0013
[3,] -0.0004  0.0013  0.0055

> sqrt(with(bladder.cox2,diag(var)/diag(naive.var)))
[1] 1.244492 1.223092 1.055761
```

These are the ratios of correct confidence intervals to naive ones.

```
> summary(bladder.cox3)
Call:
coxph(formula = bladder.surv ~ tx + num + cluster(id), data = bladder)

  n= 190, number of events= 112

        coef exp(coef) se(coef) robust se      z Pr(>|z|)
tx  -0.41172   0.66251  0.20029   0.25153 -1.637  0.10166
num  0.17001   1.18531  0.04646   0.05636  3.016  0.00256 **
---
Signif. codes:  0 *** 0.001 ** 0.01 * 0.05 . 0.1   1

    exp(coef) exp(-coef) lower .95 upper .95
tx     0.6625     1.5094    0.4047     1.085
num    1.1853     0.8437    1.0613     1.324

Concordance= 0.623  (se = 0.029 )
Rsquare= 0.073   (max possible= 0.992 )
Likelihood ratio test= 14.31  on 2 df,   p=0.0007799
Wald test            = 10.24  on 2 df,   p=0.005969
Score (logrank) test = 15.81  on 2 df,   p=0.0003696,   Robust = 10.6  p=0.005001

  (Note: the likelihood ratio and score tests assume independence of
     observations within a cluster, the Wald and robust score tests do not).
```