

Using Time Dependent Covariates and Time Dependent Coefficients in the Cox Model

Terry Therneau

Cynthia Crowson

Elizabeth Atkinson

Mayo Clinic

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1 Introduction

This vignette covers 3 different but interrelated concepts:

- An introduction to time dependent covariates, along with some of the most common mistakes.
- Tools for creating time-dependent covariates, or rather the data sets used to encode them.
- Time dependent coefficients.

2 Time dependent covariates

One of the strengths of the Cox model is its ability to encompass covariates that change over time. The practical reason that time-dependent covariates work is based on the underlying way in which the Cox model works: at each event time the program compares the current covariate values of the subject who had the event to the current values of all others who were at risk at that time. One can think of it as a lottery model, where at each death time there is a drawing to decide which subject “wins” the event. Each subject’s risk score $\exp(X\beta)$ determines how likely they are to win, e.g., how many “tickets” they have purchased for the drawing. The model tries to assign a risk score to each subject that best predicts the outcome of each drawing based on

- The risk set: which subjects are present for each event; the set of those able to “win the prize”.
- The covariate values of each subject just prior to the event time.

The model has a theoretical foundation in martingale theory, a mathematical construct which arose out of the study of games of chance. A key underlying condition for a martingale like game is that present actions depend only on the past. The decision of whether to play (is one in the risk set or not) and the size of a bet (covariates) can depend in any way on prior bets and patterns of won/lost, but cannot look into the future. If this holds then multiple properties can be proven about the resulting process.

A simple way to code time-dependent covariates uses intervals of time. Consider a subject with follow-up from time 0 to death at 185 days, and assume that we have a time dependent covariate (creatinine) that was measured at day 0, 90 and 120 with values of .9, 1.5, and 1.2 mg/dl. A way to encode that data for the computer is to break the subject's time into 3 time intervals 0-90, 90-120, 120-185, with one row of data for each interval. The data might look like the following

```

subject time1 time2 death creatinine
1      5     0    90     0         0.9
2      5    90   120     0         1.5
3      5   120   185     1         1.2

```

We read this as stating that over the interval from 0 to 90 the creatinine for subject "5" was 0.9 (last known level), and that this interval did not end in a death. The underlying code treats intervals as open on the left and closed on the right, e.g. the creatinine on exactly day 90 is 0.9. One way to think of this is that all changes for a given day (covariates or status) are recorded at the end of the day.

The key rule for time dependent covariates in a Cox model is simple and essentially the same as that for gambling: *you cannot look into the future*. A covariate may change in any way based on past data or outcomes, but it may not reach forward in time. In the above simple data set this means that we cannot add a linear interpolation between the creatinine values 0.9 and 1.5 to get a predicted value of 1.1 on day 100; on day 100 the later value of 1.5 has not yet been seen.

As an example consider a recent analysis from the Mayo Clinic study of aging (MCSA), a study which enrolled a stratified random sample from the population of Olmsted County and then has followed them forward in time. The occurrence of mild cognitive impairment (MCI), dementia, and death are all of interest. The paper starts out with a table comparing baseline covariates for those who never progress to MCI versus those who ever did, there is also a table of baseline covariates versus survival. Both of these are fine: if you think in terms of an R formula they could be written with future outcomes on the left hand side of the formula and past information on the right. A table that compared the survival of those who did or did not progress to MCI, however, would be invalid. It corresponds to a model with a future occurrence on both sides of the equation.

One of the more well known examples of this error is analysis by treatment response: at the end of a trial a survival curve is made comparing those who had an early response to treatment (shrinkage of tumor, lowering of cholesterol, or whatever) to those who did not, and it discovered that responders have a better curve. A Cox model fit to the same data will demonstrate a strong "significant" effect. The problem arises because any early deaths, those that occur before response can be assessed, will all be assigned to the non-responder group, even deaths that have nothing to do with the condition under study. Below is a simple example based on the advanced lung cancer data set. Assume that subjects came in monthly for 12 cycles of treatment, and randomly declare a "response" for 5% of the subjects at each visit.

```

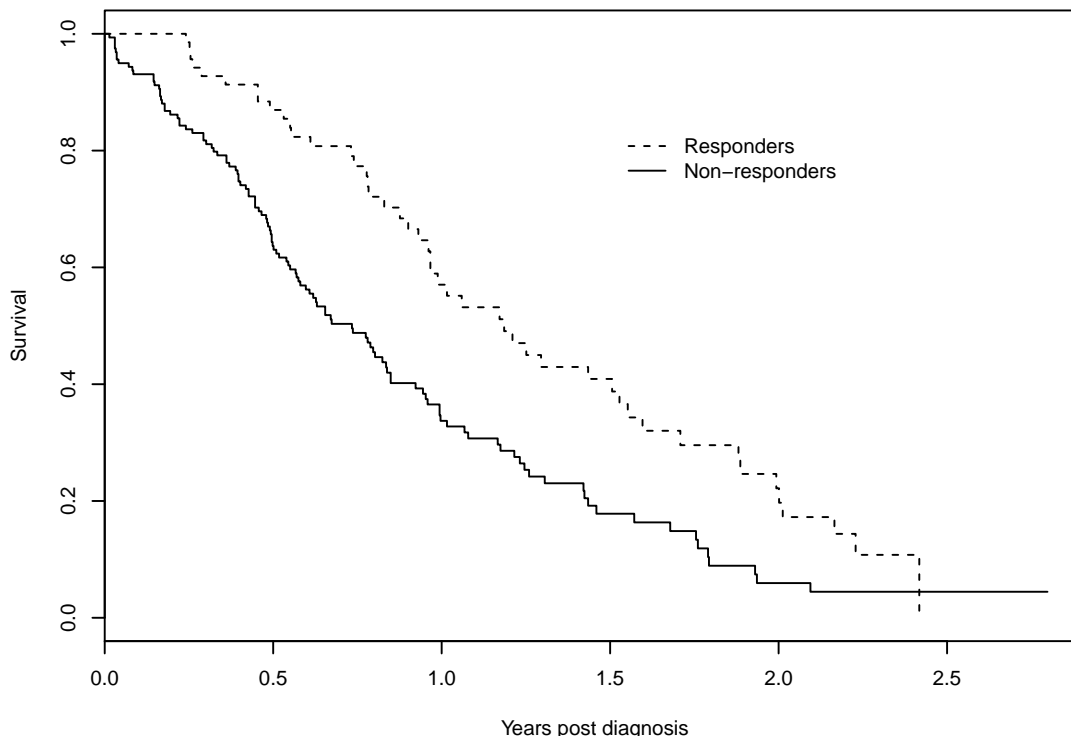
> set.seed(1953) # a good year
> nvisit <- floor(pmin(lung$time/30.5, 12))
> response <- rbinom(nrow(lung), nvisit, .05) > 0
> badfit <- survfit(Surv(time/365.25, status) ~ response, data=lung)

```

```

> plot(badfit, mark.time=FALSE, lty=1:2,
      xlab="Years post diagnosis", ylab="Survival")
> legend(1.5, .85, c("Responders", "Non-responders"),
      lty=2:1, bty='n')

```



What is most surprising about this error is the *size* of the false effect that is produced. A Cox model using the above data reports a hazard ratio of 1.9 fold with a p-value of less than 1 in 1000.

The alarm about this incorrect approach has been sounded often [1, 2, 8] but the analysis is routinely re-discovered. A slightly subtler form of the error is discussed in Redmond et al [7]. Breast cancer chemotherapy patients were divided into three groups based on whether the patient eventually received > 85%, 65–85% or < 65% of the dose planned at the start of their treatment. The chemotherapy regimen spans 12 weeks of treatment and the early deaths, not surprisingly, do not get all their dose.

If response is instead coded as a time-dependent covariate whose values depend only on the past, then the problem disappears. For treatment response this will be a variable that starts at 0 for all subjects and is recoded to 1 only when the response occurs. For dose it would measure cumulative dose to date.

There are many variations on the error: interpolation of the values of a laboratory test linearly between observation times, removing subjects who do not finish the treatment plan, imputing the date of an adverse event as midway between observation times, etc. Using future data will often generate large positive or negative bias in the coefficients, but sometimes it generates little bias at all. It is nearly impossible to predict a priori which of these will occur in any given data

set. Using such a covariate is similar to jogging across a Los Angeles freeway: disaster is not guaranteed — but it is likely.

The most common way to encode time-dependent covariates is to use the (start, stop] form of the model.

```
> fit <- coxph(Surv(time1, time2, status) ~ age + creatinine,
              data=mydata)
```

In data set `mydata` a patient might have the following observations

subject	time1	time2	status	age	creatinine	...
1	0	15	0	25	1.3	
1	15	46	0	25	1.5	
1	46	73	0	25	1.4	
1	73	100	1	25	1.6	

In this case the variable `age` = age at entry to the study stays the same from line to line, while the value of creatinine varies and is treated as 1.3 over the interval (0, 15], 1.5 over (15, 46], etc. The intervals are open on the left and closed on the right, which means that the creatinine is taken to be 1.3 on day 15. The status variable describes whether or not each interval ends in an event.

One common question with this data setup is whether we need to worry about correlated data, since a given subject has multiple observations. The answer is no, we do not. The reason is that this representation is simply a programming trick. The likelihood equations at any time point use only one copy of any subject, the program picks out the correct row of data at each time. There two exceptions to this rule:

- When subjects have multiple events, then the rows for the events are correlated within subject and a cluster variance is needed.
- When a subject appears in overlapping intervals. This however is almost always a data error, since it corresponds to two copies of the subject being present in the same strata at the same time, e.g., she could meet herself at a party.

A subject can be at risk in multiple strata at the same time, however. This corresponds to being simultaneously at risk for two distinct outcomes.

3 Building time-dependent sets with `tmerge`

3.1 The function

A useful function for building data sets is `tmerge`, which is part of the survival library. The idea is to build up a time dependent data set one endpoint at a time. The primary arguments are

- `data1`: the base data set that will be added onto
- `data2`: the source for new information
- `id`: the subject identifier in the new data

- ...: additional arguments that add variables to the data set
- tstart, tstop: used to set the time range for each subject
- options

The created data set has three new variables (at least), which are `id`, `tstart` and `tstop`.

The key part of the call are the “...” arguments which each can be one of four types: `tdc()` and `cumtdc()` add a time dependent variable, `event()` and `cumevent()` add a new endpoint. In the survival routines time intervals are open on the left and closed on the right, i.e., `(tstart, tstop]`. Time dependent covariates apply from the start of an interval and events occur at the end of an interval. If a data set already had intervals of `(0,10]` and `(10, 14]` a new time dependent covariate or event at time 8 would lead to three intervals of `(0,8]`, `(8,10]`, and `(10,14]`; the new time-dependent covariate value would be added to the second interval, a new event would be added to the first one.

The basic form of the function is

```
> newdata <- tmerge(data1, data2, id, newvar=tdc(time,value), ...)
```

Where `data1` is the starting data set and additions to the data are taken from `data2`. The idea behind the function is that each addition will be “slipped in” to the original data in the same way that one would slide a new card into an existing deck of cards. It is a complex function, and we illustrate it below with a set of examples that sequentially reveal its features.

3.2 CGD data set

Chronic granulomatous disease (CGD) is a heterogeneous group of uncommon inherited disorders characterized by recurrent pyogenic infections that usually begin early in life and may lead to death in childhood. In 1986, Genentech, Inc. conducted a randomized, double-blind, placebo-controlled trial in 128 CGD patients who received Genentech’s humanized interferon gamma (rIFN-g) or placebo three times daily for a year. Data were collected on all serious infections until the end of followup, which occurred before day 400 for most patients. One patient was taken off on the day of his last infection; all others have some followup after their last episode.

Below are the first 10 observations, see the help page for `cgd0` for the full list of variable names. The last few columns contain the duration of follow-up for the subject followed by infection times. Subject 1 was followed for 414 days and had infections on days 219 and 373, subject 2 had 7 infections and subject 3 had none.

```
1 204 082888 1 2 12 147.0 62.0 2 2 2 2 414 219 373
2 204 082888 0 1 15 159.0 47.5 2 2 1 2 439 8 26 152 241 249 322 350
3 204 082988 1 1 19 171.0 72.7 1 2 1 2 382
4 204 091388 1 1 12 142.0 34.0 1 2 1 2 388
5 238 092888 0 1 17 162.5 52.7 1 2 1 1 383 246 253
6 245 093088 1 2 44 153.3 45.0 2 2 2 2 364
7 245 093088 0 1 22 175.0 59.7 1 2 1 2 364 292
8 245 093088 1 1 7 111.0 17.4 1 2 1 2 363
9 238 100488 0 1 27 176.0 82.8 2 2 1 1 349 294
10 238 100488 1 1 5 113.0 19.5 1 2 1 1 371
```

The data set is included as `cgd0` in the `survival` library. Here is the R printout of the first four subjects.

```
> cgd0[1:4,]

  id center random treat sex age height weight inherit
1  1    204  82888     1  2  12   147   62.0         2
2  2    204  82888     0  1  15   159   47.5         2
3  3    204  82988     1  1  19   171   72.7         1
4  4    204  91388     1  1  12   142   34.0         1
  steroids propylac hos.cat futime etime1 etime2 etime3
1         2         2       2   414    219    373    NA
2         2         1       2   439     8     26   152
3         2         1       2   382    NA    NA    NA
4         2         1       2   388    NA    NA    NA
  etime4 etime5 etime6 etime7
1     NA     NA     NA     NA
2    241    249    322    350
3     NA     NA     NA     NA
4     NA     NA     NA     NA
```

We want to turn this into a data set that has survival in a counting process form.

- Each row of the resulting data set represents a time interval (time1, time2] which is open on the left and closed on the right. Covariate values for that row are the covariate values that apply over that interval.
- The event variable for each row i is 1 if the time interval ends with an event and 0 otherwise.

We don't need variables `etime1`–`etime7` in the final data set, so they are left out of the `data1` argument in the first call.

```
> dim(cgd0)

[1] 128  20

> newcgd <- tmerge(data1=cgd0[, 1:13], data2=cgd0, id=id, tstop=futime)
> newcgd <- tmerge(newcgd, cgd0, id=id, infect = event(etime1))
> newcgd <- tmerge(newcgd, cgd0, id=id, infect = event(etime2))
> newcgd <- tmerge(newcgd, cgd0, id=id, infect = event(etime3))
> newcgd <- tmerge(newcgd, cgd0, id=id, infect = event(etime4))
> newcgd <- tmerge(newcgd, cgd0, id=id, infect = event(etime5))
> newcgd <- tmerge(newcgd, cgd0, id=id, infect = event(etime6))
> newcgd <- tmerge(newcgd, cgd0, id=id, infect = event(etime7))
> newcgd <- tmerge(newcgd, newcgd, id, enum=cumtdc(tstart))
> dim(newcgd)

[1] 203  17
```

```

> newcgd[1:5,c(1, 4:6, 13:17)]

  id treat sex age futime tstart tstop infect enum
1  1     1  2  12   414     0  219     1     1
2  1     1  2  12   414   219  373     1     2
3  1     1  2  12   414   373  414     0     3
4  2     0  1  15   439     0    8     1     1
5  2     0  1  15   439     8   26     1     2

> attr(newcgd, "tcount")

      early late gap within boundary leading trailing tied
infect    0    0    0    44         0         0         0    0
infect    0    0    0    16         0         0         1    0
infect    0    0    0     8         0         0         0    0
infect    0    0    0     3         0         0         0    0
infect    0    0    0     2         0         0         0    0
infect    0    0    0     1         0         0         0    0
infect    0    0    0     1         0         0         0    0
enum      0    0    0     0         75        128         0    0

> coxph(Surv(tstart, tstop, infect) ~ treat + inherit + steroids +
+ cluster(id), newcgd)

Call:
coxph(formula = Surv(tstart, tstop, infect) ~ treat + inherit +
steroids + cluster(id), data = newcgd)

      coef exp(coef) se(coef) robust se      z      p
treat  -1.072    0.342   0.262   0.312 -3.44 0.00058
inherit  0.178    1.194   0.236   0.318  0.56 0.57639
steroids -0.773    0.462   0.517   0.469 -1.65 0.09931

```

```

Likelihood ratio test=22.5 on 3 df, p=5.15e-05
n= 203, number of events= 76

```

These lines show the canonical way to use tmerge: each call adds one more bit of information to the data set.

- The first call sets the *time range* for each subject to be from 0 (default) to last follow-up. If a later call tried to add an event outside that range, at time = -2 say, that addition would be ignored. The range can be set explicitly by using the tstop and (optional) tstart arguments, or implicitly as will be done in the heart transplant example below. This first result has 128 rows, the same number as cgd0.
- Each additional call then adds either an endpoint or a covariate, splitting individual rows of the input in two as necessary. An `event` or `cumevent` directive adds events, while a `tdc` or `cumtdc` one adds a time dependent covariate. Events happen at the ends of intervals and time-dependent covariates change at the start of an interval.

- Additions from `data2` with a missing time value are ignored.
- The result of `tmerge` is a data frame with a few extra attributes. One of these, `tcount`, is designed to help visualize the process and was printed out after the last step above. Assume that a subject already had 3 intervals of (2,5), (5,10) and (14,40). A new event added at time 1 would be “early” while one at time 50 is after any interval and would be recorded as “late”. An event at time 3 is within an interval, one at 5 is on the border of two intervals, one at 14 is at the leading edge of an interval, one at time 10 in on the trailing edge and at time 11 is in a gap. In this data set all new additions fell strictly within prior intervals. We also see that `etime6` and `etime7` each added only a single event to the data.
- If two observations in `data2` for a single person share exactly the same time, the created value will be the later contribution for `tdc()` or `event()` calls, `cumtdc()` and `cumevent()` will add. The “tied” column tells how often this happened; in some data sets this behavior might not be desired and one would need to break the ties before calling `tmerge`.
- The last `tmerge` call adds a simple time-dependent variable `enum` which is a running observation count for each subject. This can often be a useful variable in later models or processing, e.g. `enum==1` selects off the first row for each subject.
- The extra attributes of the data frame are ephemeral: they will be lost as soon as any further manipulation is done. This is intentional.
- One can verify that the resulting data set is equivalent to `cgd`, a (start, stop] version of the CGD data in the survival library which had been created by hand several years earlier.

The `tmerge` function processes arguments sequentially, and the above example can be rewritten as below. There is no computational advantage of one form versus the other.

```
> test <- tmerge(cgd0[, 1:13], cgd0, id=id, tstop=futime,
               infect = event(etime1), infect= event(etime2),
               infect = event(etime3), infect= event(etime4),
               infect = event(etime5), infect= event(etime6),
               infect = event(etime7))
> test <- tmerge(test, test, id= id, enum = cumtdc(tstart))
> all.equal(newcgd, test)
```

```
[1] TRUE
```

3.3 Stanford heart transplant

The `java` data set contains information from the Stanford heart transplant study, in the form that it appeared in the paper of Crowley and Hu [3]. The data set has one line per subject which contains the baseline covariates along with dates of enrollment, transplant, and death or last follow-up. We want to create `transplant` as a time dependent covariate. As is often the case with real data, this data set contains a few anomalies that need to be dealt with when setting up an analysis data set.

1. One subject died on the day of entry. However (0,0) is an illegal time interval for the `coxph` routine. It suffices to have them die on day 0.5. An alternative is to add 1 day to everyone's follow-up, e.g., subject 2 who enrolled on Jan 2 1968 and died on Jan 7 would be credited with 6 days. (This is what Kalbfleisch and Prentice do in their textbook.) The result of the final `coxph` call is the same from either strategy.
2. A subject transplanted on day 10 is considered to have been on medical treatment for days 1–10 and as transplanted starting on day 11. That is, except for patient 38 who died on the same day as their procedure. They should be treated as a transplant death; the problem is resolved by moving this transplant back .5 day.
3. The treatment coefficients in table 6.1 of the definitive analysis found in Kalbfleisch and Prentice [5] will only be obtained if covariates are defined in precisely the same way, since their models include interactions. (Table 5.2 in the original edition of the book). For age this is (age in days)/ 365.25 - 48 years, and for year of enrollment it is the number of years since the start of the study: (entry date - 1967/10/1)/365.25. (Until I figured this out I would get occasional "why is coxph giving the wrong answers" emails.)

Since time is in days the fractional time of 0.5 could be any value between 0 and 1, our choice will not affect the results.

```
> jasa$subject <- 1:nrow(jasa) #we need an identifier variable
> tdata <- with(jasa, data.frame(subject = subject,
                                futime= pmax(.5, fu.date - accept.dt),
                                txtime= ifelse(tx.date== fu.date,
                                                (tx.date -accept.dt) -.5,
                                                (tx.date - accept.dt)),
                                fustat = fustat
                                ))
> sdata <- tmerge(jasa, tdata, id=subject,
                 death = event(futime, fustat),
                 trt    = tdc(txtime),
                 options= list(idname="subject"))
> attr(sdata, "tcount")

      early late gap within boundary leading trailing tied
death    0    0    0     0         0         0       103    0
trt      0    0    0    67         0         2         0    0

> sdata$age <- sdata$age -48
> sdata$year <- as.numeric(sdata$accept.dt - as.Date("1967-10-01"))/365.25
> # model 6 of the table in K&P
> coxph(Surv(tstart, tstop, death) ~ age*trt + surgery + year,
        data= sdata, ties="breslow")
```

Call:

```
coxph(formula = Surv(tstart, tstop, death) ~ age * trt + surgery +
      year, data = sdata, ties = "breslow")
```

	coef	exp(coef)	se(coef)	z	p
age	0.0153	1.0154	0.0175	0.87	0.383
trt	0.0446	1.0456	0.3217	0.14	0.890
surgery	-0.6211	0.5373	0.3679	-1.69	0.091
year	-0.1361	0.8728	0.0709	-1.92	0.055
age:trt	0.0270	1.0274	0.0271	1.00	0.319

Likelihood ratio test=16.1 on 5 df, p=0.00669
n= 170, number of events= 75

This example shows a special case for the `tmerge` function that is quite common: if the first created variable is an event then the time range for each subject is inferred to be from 0 to the event time: explicit `tstop` and `tstart` arguments are not required. It also makes use of a two argument form of `event`. Each of the `event`, `cumevent`, `tdc` and `cumtdc` functions may have a second argument, which if present will be used as the value for the event code or time dependent covariate. If this second argument is not present a value of 1 is used.

If a created variable is not already in `data1`, the starting value *before* the first definition of that variable is a NA for a `tdc` or `cumtdc` call that has two arguments and 0 in all other cases. If the variable being created is already a part of `data1`, then our updates make changes to that variable. Be careful of this. This feature is what allowed for the `infection` indicator to be build up incrementally in the `cgd` example above, but quite surprising results can occur when you think a new variable is being created de novo but its name is already in use. For example, if we name the new variable ‘transplant’ in the third line of `sdata` above it collides with an existing variable in the `java` data set; the result is to not create a time-dependent transplant variable at all. (The author made this mistake himself when creating this vignette, and then spent several hours searching the `tmerge` code for an error that wasn’t there.)

The `tcount` table for the above fit shows all the deaths at the trailing edge of their interval, which is expected since the time of death or last follow-up was used to define each subject’s interval of risk. Two of the transplants happened on day 0 and are listed as occurring on the leading edge of the first follow-up interval for the subject. The other 67 transplants were strictly within the (0, last follow up) interval of each subject.

3.4 PBC data

The `pbc` data set contains baseline data and follow-up status for a set of subjects with primary biliary cirrhosis, while the `pbcseq` data set contains repeated laboratory values for those subjects. The first data set contains data on 312 subjects in a clinical trial plus 106 that agreed to be followed off protocol, the second data set has data only on the trial subjects.

```
> temp <- subset(pbc, id <= 312, select=c(id:sex, stage)) # baseline
> pbc2 <- tmerge(temp, temp, id=id, death = event(time, status)) #set range
> pbc2 <- tmerge(pbc2, pbcseq, id=id, ascites = tdc(day, ascites),
               bili = tdc(day, bili), albumin = tdc(day, albumin),
               protime = tdc(day, protime), alk.phos = tdc(day, alk.phos))
> fit1 <- coxph(Surv(time, status==2) ~ log(bili) + log(protime), pbc)
```

```
> fit2 <- coxph(Surv(tstart, tstop, death==2) ~ log(bili) + log(prottime), pbc2)
> rbind('baseline fit' = coef(fit1),
       'time dependent' = coef(fit2))
```

```

           log(bili) log(prottime)
baseline fit  0.930592  2.890573
time dependent 1.241214  3.983400
```

We start the build with a baseline data set that has a subset of the variables. This is due to my own frugality — I happen to like data sets that are more trim. It is not a requirement of the `tmerge` function, however, and a user is certainly free to skip the first step above and build `pbc2` directly from data set `pbc`.

The coefficients of bilirubin and prothrombin time are somewhat larger in the time-dependent analysis than the fit using only baseline values. In this autoimmune disease there is steady progression of liver damage, accompanied by a steady rise in these two markers of dysfunction. The baseline analysis captures patients' disease status at the start, the time-dependent analysis is able to account for those who progress more quickly. In the `pbc` data set the status variable is 0= censored, 1= liver transplant and 2= death; the above analyses were models of time to death, censoring at transplant. (At the time of the PBC study liver transplantation was still in its infancy and it is fair to view the 19/312 subjects who received the procedure as a random sample. In the modern era there are far more waiting recipients than organs and available livers are directed to those patients whose illness is most dire; censoring at transplant would not lead to an interpretable result.)

By default `tmerge` ignores any updates from `data2` that have a missing value for either the time or the value. In the `pbcseq` data set there are several observations with a missing alkaline phosphatase value. A consequence of this behavior is that the `pbc2` data set effectively uses “last value carried forward” values for `alk.phos`, replacing those missing values. Subject 6 for instance has a total follow-up of 2503, and `alk.phos` values of 682 and NA on days 1492 and 2453, respectively; in the final data set it is coded 682 from day 1492 until last follow up. One can change this default by adding `options=list(na.rm=FALSE)` to the second call above, in which case the alkaline phosphatase value over the interval (2453, 2503] will become missing. Any `tdc` calls with a missing time are still ignored, independent of the `na.rm` value, since we would not know where to insert them.

```
> attr(pbc2, "tcount")
```

```

           early late gap within boundary leading trailing
death      0    0  0     0          0        0        312
ascites    0  131  0   1442         0       312        0
bili       0  138  0    53       1442     312        0
albumin    0  138  0    0       1495     312        0
prottime   0  138  0    0       1495     312        0
alk.phos   0  131  0    0       1442     312        0
tied
death      0
ascites    0
bili       0
```

```
albumin      0
protime      0
alk.phos     0
```

The tcount results are interesting. For the first addition of ascites we have 312 observations on a leading edge of follow up, which is all of the baseline lab values at time 0, and 1442 further additions within the subjects' follow-up interval. The latter cause a new break point to be added at each of these intermediate laboratory dates, for subsequent additions these 1442 times lie on a boundary of two intervals. Another 131 non-missing alkaline phosphatase values occurred after the last follow-up date of the pbc data set and are ignored. Bilirubin is missing on no subjects, so it's addition creates a few more unique break points in the follow-up, namely those clinical visits for which the ascites value was missing.

The data for the pbcseq data set was assembled at a later calendar time than the primary data set. Since having lab test results is a certain marker that the patient is still alive, would a better analysis have used this test information to extend the last follow-up date for these 138 "late" subjects with a later laboratory date? Not necessarily.

Odd things happen in survival analysis when risk sets are extended piecemeal. A basic tenet of the Cox model is that if someone is marked as being "at risk" over some interval (s, t) , this means that "if they had had an event over that interval, we would have recorded it." Say someone ended their initial follow-up time at 3000 days and then had a lab test at 3350 days (subjects returned about once a year). If we only extend the time of those who had a test, then saying that this subject was at risk during the interval (3000, 3350) is false: if they had died in that interval, they would not have had the lab test and would not obtained the extension, nor would their death have been updated in the original pbc data set. The cutoff rule of `tmerge` is purposefully conservative to avoid creating such anomalies.

In the case of the PBC data set this author happens to know that active follow-up *was* continued for all subjects, both those that did and did not return for further laboratory tests. This updated follow-up information is included in the pbcseq data and could have been used to set a wider time range. Such is not always the case, however. Automatic additions to a data set via electronic systems can be particularly troublesome. One case from the author's experience involved a study of patient outcomes after organ transplant. Cases were actively followed up for 3 years, at which time priorities shifted and the clerical staff responsible for the active follow-up were reassigned. Automatic updates from a state death index continued to accumulate, however. A Kaplan-Meier curve computed at 5 years showed the remarkable result of a 3 year survival of .9 followed by a precipitous drop to 0 at 5 years! This is because there was, by definition, 100% mortality in all those subjects with more than 3 years of supposed follow-up.

3.5 Time delay and other options

The `options` argument to the `tmerge` routine is a list with one or more of the following five elements, listed below along with their default values.

- `idname = 'id'`
- `tstartname = 'tstart'`
- `tstopname = 'tstop'`

- `na.rm = TRUE`
- `delay = 0`

The first three of these are the variable names that will be used for the identifier, start, and stop variables which are added to the output data set. They only need to be specified one time within a series of `tmerge` calls in order to effect a change. The `na.rm` option has been discussed above; it affects `tdc()` and `cumtdc()` directives within a single `tmerge` call. The `delay` option causes any `tdc` or `cumtdc` action in the `tmerge` call to be delayed by a fixed amount. The final two `tmerge` calls below are *almost* identical in their action:

```
> temp <- subset(pbc, id <= 312, select=c(id:sex, stage))
> pbc2 <- tmerge(temp, temp, id=id, death = event(time, status))
> pbc2a <- tmerge(pbc2, pbcseq, id=id, ascites = tdc(day, ascites),
  bili = tdc(day, bili), options= list(delay=14))
> pbc2b <- tmerge(pbc2, pbcseq, id=id, ascites = tdc(day+14, ascites),
  bili = tdc(day+14, bili))
```

The difference between `pbc2a` and `pbc2b` is that the first call does not defer baseline values for each subject, i.e., any value with a time that is on or before the the subject's first time point, as that will introduce intervals with a missing value into the result.

The more important question is *why* one would wish to delay or lag a time dependent covariate. One reason is to check for cases of reverse causality. It is sometimes the case that a covariate measured soon before death is not a predictor of death but rather is simply a marker for an event that is already in progress. A simple example would be the time dependent covariate “have called the family for a final visit”. A less obvious one from the author's experience occurs when a clinical visit spans more than one day, the endpoint is progression, and one or more laboratory results that were used to define “progression” get recorded in the data set 1-2 days before the progression event. (They were perhaps pulled automatically from a laboratory information system). One then ends up with the tautology of a test value predicting its own result.

Even more subtle biases can occur via coding errors. For any data set containing constructed time-dependent covariates, it has become the author's practice to re-run the analyses after adding a 7-14 day lag to key variables. When the results show a substantial change, and this is not infrequent, understanding why this occurred is an critical step. Even if there is not an actual error, one has to question the value of a covariate that can predict death within the next week but fails for a longer horizon.

3.6 Cumulative events

The action of the `cumevent` operator is different than `cumtdc` in several ways. Say that we have a subject with outcomes of one type at times 5, 10, and 15 and another type at times 6 and 15, with a follow-up interval of 0 to 20. For illustration I'll call the first event 'athsma' and the second 'IBD' (a disease flare in inflammatory bowel disease). A resulting data set would have the following form:

interval	cumtdc		cumevent	
	athsma	IBD	athsma	IBD
(0, 5]	0	0	1	0
(5, 6]	1	0	0	1
(6, 10]	1	1	2	0
(10, 15]	2	1	3	2
(15, 20]	3	2	0	0

Events happen at the ends of an interval and time-dependent covariates change the following intervals. More importantly, time-dependent covariates persist while events do not, a `cumevent` action simply changes the label attached to an event.

3.6.1 REP

The motivating case for `tmerge` came from a particular problem: the Rochester Epidemiology Project has tracked all subjects living in Olmsted County, Minnesota, from 1965 to the present. For an investigation of cumulative comorbidity we had three data sets

- base: demographic data such as sex and birth date
- timeline: one or more rows for each subject containing age intervals during which they were a resident of the county. The important variables are `id`, `age1` and `age2`; each (`age1`, `age2`) pair marks an interval of residence. Disjoint intervals are not uncommon.
- outcome: one row for the first occurrence of each outcome of interest. The outcomes were 20 comorbid conditions as defined by a particular research initiative from the National Institutes of Health.

The structure for building the data is shown below. (The data for this example unfortunately cannot be included with the survival library so the code is shown but not executed.)

```
> newd <- tmerge(data1=base, data2=timeline, id=repid, tstart=age1,
                 tstop=age2, options(id="repid"))
> newd <- tmerge(newd, outcome, id=repid, mcount = cumtdc(age))
> newd <- tmerge(newd, subset(outcome, event='diabetes'),
                 diabetes= tdc(age))
> newd <- tmerge(newd, subset(outcome, event='arthritis'),
                 arthritis= tdc(age))
```

The first call to `tmerge` adds the time line for each observation to the baseline data. For this first call both `data1` and `data2` must contain a copy of the `id` variable (here `repid`), and `data1` is constrained to have only a single line for each `id` value. (Subjects have a single baseline.) Each subsequent call adds a new variable to the data set. The second line creates a covariate which is a cumulative count of the number of comorbidities thus far for each subject. The third line creates a time dependent covariate (`tdc`) which will be 0 until the age of diabetes and is 1 thereafter, the fourth line creates a time dependent variable for the presence of arthritis.

Time dependent covariates that occur before the start of a subject's follow-up interval or during a gap in time do not generate a new time point, but they do set the value of that

covariate for future times. Events that occur in a gap are not counted. The rationale is that during a subject’s time within the county we would like the variable “prior diagnosis of diabetes” to be accurate, even if that diagnosis occurred during a prior period when the subject was not a resident. For events outside of the time line, we have no way to know who the appropriate comparison group is, and so must ignore those events. (Formally, the risk set would be the set of all non-residents who, if they were to have had an event at the same age, we would find out about it because they will later move to the county, have a medical encounter here, and have that event written into the “prior conditions” section of their medical record.)

4 Time dependent coefficients

Time dependent covariates and time dependent coefficients are two different extensions of a Cox model, as shown in the two equations below.

$$\lambda(t) = \lambda_0(t)e^{\beta X(t)} \tag{1}$$

$$\lambda(t) = \lambda_0(t)e^{\beta(t)X} \tag{2}$$

Equation (1) is a time dependent covariate, a commonly used and well understood usage. Equation (2) has a time dependent coefficient. These models are much less common, but represent one way to deal with non-proportional hazards – the proportional hazard assumption is precisely that the coefficient does not change over time: $\beta(t) = c$. The `cox.zph` function will plot an estimate of $\beta(t)$ for a study and is used to diagnose and understand non-proportional hazards. Here for example is a test case using the veterans cancer data.

```
> options(show.signif.stars = FALSE) # display user intelligence
> vfit <- coxph(Surv(time, status) ~ trt + prior + karno, veteran)
> vfit
```

Call:

```
coxph(formula = Surv(time, status) ~ trt + prior + karno, data = veteran)
```

	coef	exp(coef)	se(coef)	z	p
trt	0.18020	1.19745	0.18347	0.98	0.33
prior	-0.00555	0.99446	0.02023	-0.27	0.78
karno	-0.03377	0.96679	0.00511	-6.60	4e-11

```
Likelihood ratio test=43 on 3 df, p=2.41e-09
n= 137, number of events= 128
```

```
> quantile(veteran$karno)
```

0%	25%	50%	75%	100%
10	40	60	75	99

```
> zp <- cox.zph(vfit, transform= function(time) log(time +20))
> zp
```

```

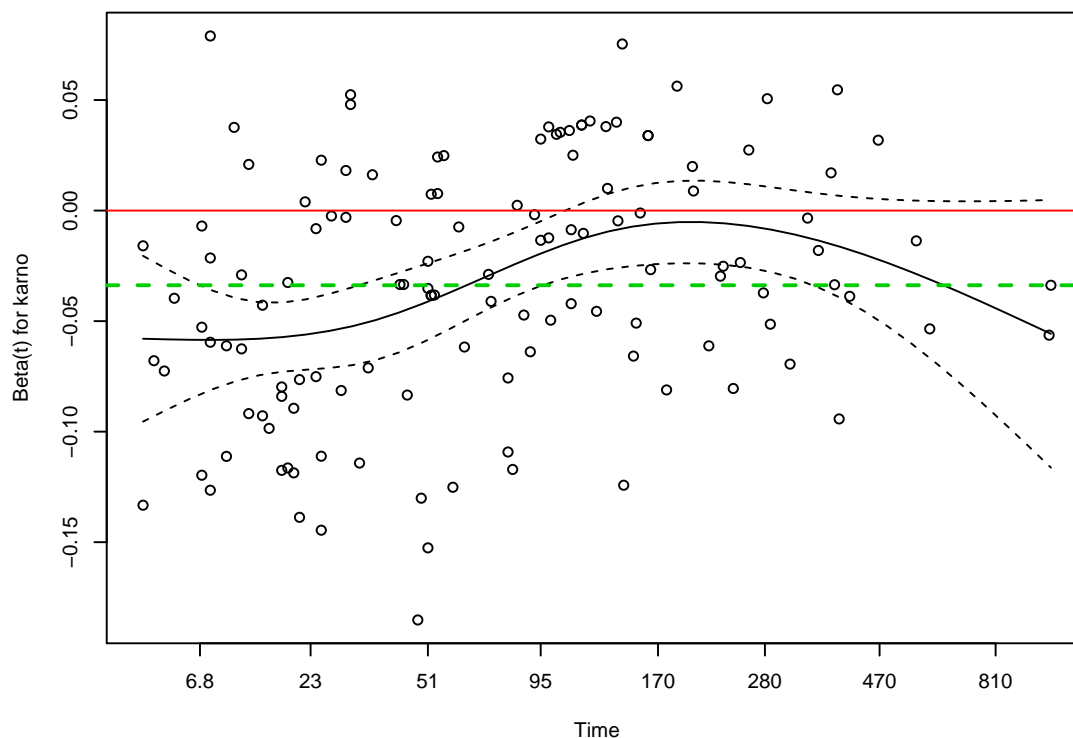
      rho  chisq      p
trt    -0.0598  0.477 0.48976
prior  -0.1535  3.213 0.07307
karno   0.2890  9.951 0.00161
GLOBAL      NA 12.133 0.00694

```

```

> plot(zp[3]) # a plot for the 3rd variable in the fit
> abline(0,0, col=2)
> abline(h= vfit$coef[3], col=3, lwd=2, lty=2)

```



Karnofsky score is a very important predictor, but its effect is not constant over time as shown by both the test and the plot. Early on it has a large negative effect: the risk of someone at the first quartile is approximately $\exp(35 \cdot 0.03377) = 3.2$ fold times that of someone at the third quartile, but by 200 days this has waned and is not much different from zero. One explanation is that, in this very acute illness, any measure that is over 6 months old is no longer relevant.

The proportional hazards model estimates an average hazard over time, the value of which is shown by the dashed horizontal line. The use of an average hazard is often reasonable, the proportional hazards assumption is after all never precisely true. In this case, however, the departure is quite large and a time dependent coefficient is a more useful summary of the actual state. The `cox.zph` plot is excellent for diagnosis but does not, however, produce a formal fit of $\beta(t)$. What if we want to fit the model?

4.1 Step functions

One of the simplest extensions is a step function for $\beta(t)$, i.e., different coefficients over different time intervals. An easy way to do this is to use the `survSplit` function to break the data set into time dependent parts. We will arbitrarily divide the veteran's data into 3 epochs of the first 3 months, 3-6 months, and greater than 6 months.

```
> vet2 <- survSplit(Surv(time, status) ~ ., data= veteran, cut=c(90, 180),
                    episode= "tgroup", id="id")
> vet2[1:7, c("id", "tstart", "time", "status", "tgroup", "age", "karno")]
```

	id	tstart	time	status	tgroup	age	karno
1	1	0	72	1	1	69	60
2	2	0	90	0	1	64	70
3	2	90	180	0	2	64	70
4	2	180	411	1	3	64	70
5	3	0	90	0	1	38	60
6	3	90	180	0	2	38	60
7	3	180	228	1	3	38	60

The first subject died at 72 days, his data is unchanged. The second and third subjects contribute time to each of the three intervals.

```
> vfit2 <- coxph(Surv(tstart, time, status) ~ trt + prior +
                 karno:strata(tgroup), data=vet2)
> vfit2
```

Call:

```
coxph(formula = Surv(tstart, time, status) ~ trt + prior + karno:strata(tgroup),
      data = vet2)
```

	coef	exp(coef)	se(coef)
trt	-0.01103	0.98904	0.18906
prior	-0.00611	0.99391	0.02035
karno:strata(tgroup)tgroup=1	-0.04875	0.95241	0.00622
karno:strata(tgroup)tgroup=2	0.00805	1.00808	0.01282
karno:strata(tgroup)tgroup=3	-0.00835	0.99169	0.01462

	z	p
trt	-0.06	0.95
prior	-0.30	0.76
karno:strata(tgroup)tgroup=1	-7.84	4.7e-15
karno:strata(tgroup)tgroup=2	0.63	0.53
karno:strata(tgroup)tgroup=3	-0.57	0.57

Likelihood ratio test=63 on 5 df, p=2.86e-12
n= 225, number of events= 128

```
> cox.zph(vfit2)
```

	rho	chisq	p
trt	-0.0893	1.1044	0.2933
prior	-0.1645	3.6083	0.0575
karno:strata(tgroup)tgroup=1	0.0333	0.1084	0.7419
karno:strata(tgroup)tgroup=2	-0.0212	0.0431	0.8355
karno:strata(tgroup)tgroup=3	0.0208	0.0496	0.8237
GLOBAL	NA	5.0675	0.4077

A fit to the revised data shows that the effect of baseline Karnofsky score is essentially limited to the first two months. The `cox.zph` function shows no further time dependent effect of Karnofsky score. This last is of course no surprise, since we used the original graph to pick the cut points. A “test” that the coefficients for the three intervals are different will be biased by this sequential process and should be viewed with caution.

Survival curves post fit require a little more care. The default curve uses the mean covariate values, which is always problematic and completely useless in this case. Look at the set of saved means for the model:

```
> vfit2$means
```

	trt	prior
	1.471111	2.977778
karno:strata(tgroup)tgroup=1	karno:strata(tgroup)tgroup=2	
	35.662222	19.022222
karno:strata(tgroup)tgroup=3		
	8.444444	

The default curve will be for someone on treatment arm 1.47, which applies to no one, and a single set of “blended” values of the Karnofsky score, each times the three Karnofsky coefficients. This is easily rectified by creating a new data set with time intervals.

```
> quantile(veteran$karno)
```

0%	25%	50%	75%	100%
10	40	60	75	99

```
> cdata <- data.frame(tstart= rep(c(0,30,60), 2),
                      time = rep(c(30,60, 100), 2),
                      status= rep(0,6), #necessary, but ignored
                      tgroup= rep(1:3, 2),
                      trt = rep(1,6),
                      prior= rep(0,6),
                      karno= rep(c(40, 75), each=3),
                      curve= rep(1:2, each=3))
```

```
> cdata
```

	tstart	time	status	tgroup	trt	prior	karno	curve
1	0	30	0	1	1	0	40	1
2	30	60	0	2	1	0	40	1

```

3    60 100    0    3  1    0   40    1
4     0  30    0    1  1    0   75    2
5    30  60    0    2  1    0   75    2
6    60 100    0    3  1    0   75    2

```

```

> sfit <- survfit(vfit2, newdata=cdata, id=curve)
> km <- survfit(Surv(time, status) ~ I(karno>60), veteran)
> plot(km, xmax=120, col=1:2, lwd=2,
       xlab="Days from enrollment", ylab="Survival")
> lines(sfit, col=1:2, lty=2, lwd=2)

```

In the new data set the `tgroup` variable correctly tracks time intervals. The default behavior for survival curves based on a `coxph` model is to create one curve for each line in the input data; the `id` option causes it to use a set of lines for each curve. Karnofsky scores at the 25th and 75th percentiles roughly represent the average score for the lower half of the subjects and that for the upper half, respectively, and are plotted over the top of the Kaplan-Meier curves for those below and above the median. At 30 days the Cox model curves essentially become parallel.

4.2 Continuous time-dependent coefficients

If $\beta(t)$ is assumed to have a simple functional form we can fool an ordinary Cox model program in to doing the fit. The particular form $\beta(t) = a + b \log(t)$ has for instance often been assumed. Then $\beta(t)x = ax + b \log(t)x = ax + bz$ for the special time dependent covariate $z = \log(t)x$. The time scale for the `cox.zph` plot used further above of $\log(t + 20)$ was chosen to make the first 200 days of the plot roughly linear. Per the figure this simple linear model does not fit over the entire range, but we will forge ahead and use it as an example anyway. (After all, most who fit the $\log(t)$ form have not bothered to even look at a plot.) An obvious but incorrect approach is

```

> vfit3 <- coxph(Surv(time, status) ~ trt + prior + karno +
                I(karno * log(time + 20)), data=veteran)

```

This mistake has been made often enough the the `coxph` routine has been updated to print an error message for such attempts. The issue is that the above code does not actually create a time dependent covariate, rather it creates a time-static value for each subject based on their value for the covariate `time`; no differently than if we had constructed the variable outside of a `coxph` call. This variable most definitely breaks the rule about not looking into the future, and one would quickly find the circularity: large values of `time` predict long survival, because long survival leads to large values for `time`.

A true time-dependent covariate can be constructed using the *time-transform* functionality of `coxph`.

```

> vfit3 <- coxph(Surv(time, status) ~ trt + prior + karno + tt(karno),
                data=veteran,
                tt = function(x, t, ...) x * log(t+20))
> vfit3

```

Call:

```
coxph(formula = Surv(time, status) ~ trt + prior + karno + tt(karno),
```

```

data = veteran, tt = function(x, t, ...) x * log(t + 20))

      coef exp(coef) se(coef)      z      p
trt      0.01648   1.01661  0.19071  0.09  0.9311
prior    -0.00932   0.99073  0.02030 -0.46  0.6462
karno    -0.12466   0.88279  0.02879 -4.33 1.5e-05
tt(karno) 0.02131   1.02154  0.00661  3.23  0.0013

```

```

Likelihood ratio test=53.8 on 4 df, p=5.7e-11
n= 137, number of events= 128

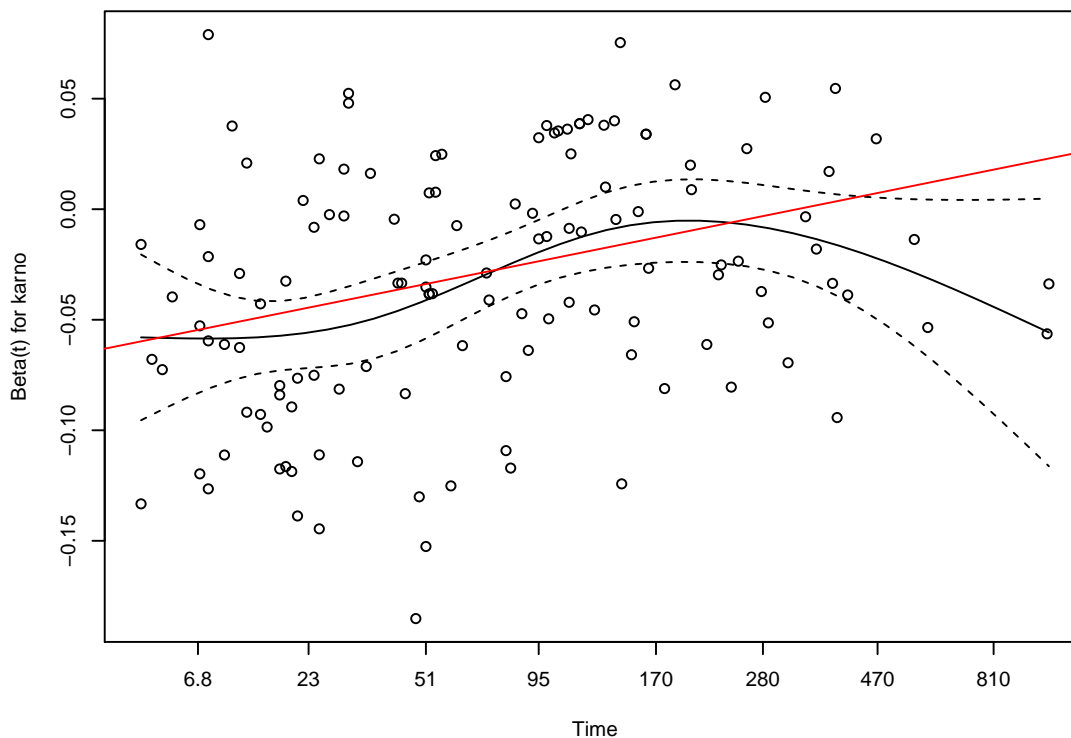
```

The time dependent coefficient is estimated to be $\beta(t) = -0.125 + 0.021 * \log(t + 20)$. We can add said line to the `cox.zph` plot. Not surprisingly, the result is rather too high for time > 200 and underestimates the initial slope. Still the fit is better than a horizontal line, as confirmed by the p-value for the slope term in `vfit3`. (The p-value for that term from `cox.zph` is nearly identical, as it must be, since the tests in `cox.zph` are for a linear effect on the chosen time scale.)

```

> plot(zp[3])
> abline(coef(vfit3)[3:4], col=2)

```



This same coding dichotomy exists in SAS phreg, by the way. Adding `time` to the right hand side of the model statement will create the time-fixed (incorrect) variable, while a programming statement within phreg that uses `time` as a variable will generate time-dependent objects. The

error is less likely there because phreg's model statement has no equivalent to the I() function, i.e., you cannot simply write "log(time)" on the right hand side.

5 Predictable time-dependent covariates

Occasionally one has a time-dependent covariate whose values in the future are predictable. The most obvious of these is patient age, occasionally this may also be true for the cumulative dose of a drug. If age is entered as a linear term in the model, then the effect of changing age can be ignored in a Cox model, due to the structure of the partial likelihood. Assume that subject i has an event at time t_i , with other subject $j \in R_i$ at risk at that time, with a denoting age. The partial likelihood term is

$$\frac{e^{\beta * a_i}}{\sum_{j \in R_i} e^{\beta * a_j}} = \frac{e^{\beta * (a_i + t_i)}}{\sum_{j \in R_i} e^{\beta * (a_j + t_i)}}$$

We see that using time-dependent age (the right hand version) or age at baseline (left hand), the partial likelihood term is identical since $\exp(\beta t_i)$ cancels out of the fraction. However, if the effect of age on risk is *non-linear*, this cancellation does not occur.

Since age changes continuously, we would in theory need a very large data set to completely capture the effect, an interval per day to match the usual resolution for death times. In practice this level of resolution is not necessary; though we all grow older, risk does not increase so rapidly that we need to know our age to the day!

One method to create a time-changing covariate is to use the *time-transform* feature of coxph. Below is an example using the pbc data set. The longest follow-up time in that data set is over 13 years, follow-up time is in days, and we might worry that the intermediate data set would be huge. The program only needs the value of the time dependent covariate(s) for each subject at the times of events, however, so the maximum number of rows in the intermediate data set is the number of subjects times the number of unique event times.

```
> pfit1 <- coxph(Surv(time, status==2) ~ log(bili) + ascites + age, pbc)
> pfit2 <- coxph(Surv(time, status==2) ~ log(bili) + ascites + tt(age),
  data=pbcc,
  tt=function(x, t, ...) {
    age <- x + t/365.25
    cbind(age=age, age2= (age-50)^2, age3= (age-50)^3)
  })
> pfit2
```

Call:

```
coxph(formula = Surv(time, status == 2) ~ log(bili) + ascites +
  tt(age), data = pbcc, tt = function(x, t, ...) {
  age <- x + t/365.25
  cbind(age = age, age2 = (age - 50)^2, age3 = (age - 50)^3)
  })
```

```
coef exp(coef) se(coef) z p
```

```

log(bili)      1.05e+00  2.85e+00  9.45e-02 11.09 < 2e-16
ascites       1.29e+00  3.64e+00  2.63e-01  4.91 9.2e-07
tt(age)age    6.66e-02  1.07e+00  1.47e-02  4.53 5.8e-06
tt(age)age2   3.04e-04  1.00e+00  1.24e-03  0.24  0.807
tt(age)age3  -9.17e-05  1.00e+00  5.00e-05 -1.83  0.067

```

```

Likelihood ratio test=179 on 5 df, p=0
n= 312, number of events= 125
(106 observations deleted due to missingness)

```

```
> anova(pfit2)
```

```
Analysis of Deviance Table
```

```
Cox model: response is Surv(time, status == 2)
Terms added sequentially (first to last)
```

	loglik	Chisq	Df	Pr(> Chi)
NULL	-639.97			
log(bili)	-956.62	-633.304	1	1
ascites	-939.07	35.098	1	3.135e-09
tt(age)	-550.50	777.133	3	< 2.2e-16

```
> # anova(pfit1, pfit2) #this fails
```

```
> 2*(pfit2$loglik - pfit1$loglik)[2]
```

```
[1] 10.80621
```

Since initial age is in years and time is in days, it was important to scale within the `pspline` function. The likelihood ratio of 10.8 on 2 degrees of freedom shows that the additional terms are mildly significant.

When there are one or more terms on the right hand side of the equation marked with the `tt()` operator, the program will pre-compute the values of that variable for each unique event time. A user-defined function is called with arguments of

- the covariate: whatever is inside the `tt()` call
- the event time
- the event number: if there are multiple strata and the same event time occurs in two of them, they can be treated separately
- the weight for the observation, if the call used weights

There is a single call to the function with a large x vector, it contains an element for each subject at risk at each event time. If there are multiple `tt()` terms in the formula, then the `tt` argument should be a list of functions with the requisite number of elements.

There are other interesting uses for the time-transform capability. One example is O'Brien's logit-rank test procedure [6]. He proposed replacing the covariate at each event time with a logit transform of its ranks. This removes the influence of any outliers in the predictor x . For this case we ignore the event time argument and concentrate on the groupings.

```

> function(x, t, riskset, weights){
  obrien <- function(x) {
    r <- rank(x)
    (r-.5)/(.5+length(r)-r)
  }
  unlist(tapply(x, riskset, obrien))
}

function(x, t, riskset, weights){
  obrien <- function(x) {
    r <- rank(x)
    (r-.5)/(.5+length(r)-r)
  }
  unlist(tapply(x, riskset, obrien))
}

```

This relies on the fact that the input arguments to `tt()` are ordered by the event number or risk set. This function is used as a default if no `tt` argument is present in the `coxph` call, but there are `tt` terms in the model formula. (Doing so allowed me to depreciate the `survobrien` function).

Another interesting usage is to replace the data by simple ranks, not rescaled to 0–1.

```

> function(x, t, riskset, weights)
  unlist(tapply(x, riskset, rank))

function(x, t, riskset, weights)
  unlist(tapply(x, riskset, rank))

```

The score statistic for this model is $(C - D)/2$, where C and D are the number of concordant and discordant pairs, see the `survConcordance` function. The score statistic from this fit is then a test for significance of the concordance statistics, and is in fact the basis for the standard error reported by `survConcordance`. The O'Brien test can be viewed as concordance statistic that gives equal weight to each event time, whereas the standard concordance weights each event proportionally to the size of the risk set. (The Cox score statistic depends on the mean x at each event time; since ranks go from 1 to number at risk the mean also scales.)

Although handy, the computational impact of the `tt` argument should be considered before using it. The Cox model requires computation of a weighted mean and variance of the covariates at each event time, a process that is inherently $O(ndp^2)$ where n = the sample size, d = the number of events and p = the number of covariates. Much of the algorithmic effort in `coxph()` is to use updating methods for the mean and variance matrices, reducing the compute time to $O((n+d)p^2)$. When a `tt` term appears updating is not possible; for even moderate size data sets the impact of nd versus $n+d$ can be surprising.

The time-transform is a new addition and still has some rough edges. At this moment the $x = TRUE$ argument is needed to get proper residuals and predicted values, and `termplot` is unable to properly reconstruct the data to plot a fit. Please communicate any concerns or interesting examples to the author.

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