A package for survival analysis in R

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Contents

Chapter 1

Introduction

1.1 History

Work on the survival package began in 1985 in connection with the analysis of medical research data, without any realization at the time that the work would become a package. Eventually, the software was placed on the Statlib repository hosted by Carnegie Mellon University. Multiple version were released in this fashion but I don't have a list of the dates — version 2 was the first to make use of the `print` method that was introduced in 'New S' in 1988, which places that release somewhere in 1989. The library was eventually incorporated directly in S-Plus, and from there it became a standard part of R.

I suspect that one of the primary reasons for the package's success is that all of the functions have been written to solve real analysis questions that arose from real data sets; theoretical issues were explored when necessary but they have never played a leading role. As a statistician in a major medical center, the central focus of my department is to advance medicine; statistics is a tool to that end. This also highlights one of the deficiencies of the package: if a particular analysis question has not yet arisen in one of my studies then the survival package will also have nothing to say on the topic. Luckily, there are many other R packages that build on or extend the survival package, and anyone working in the field (the author included) can expect to use more packages than just this one. I certainly never foresaw that the library would become as popular as it has.

This vignette is an introduction to version 3.x of the survival package. We can think of versions 1.x as the S-Plus era and $2.1 - 2.44$ as maturation of the package in R. Version 3 had 4 major goals.

- Make multi-state curves and models as easy to use as an ordinary Kaplan-Meier and Cox model.
- Deeper support for absolute risk estimates.
- Consistent use of robust variance estimates.
- Clean up various naming inconsistencies that have arisen over time.

With over 600 dependent packages in 2019, not counting Bioconductor, other guiding lights of the change are

- We can't do everything (so don't try).
- Allow other packages to build on this one. That means clear documentation of all of the results that are produced, the use of simple S3 objects that are easy to manipulate, and setting up many of the routines as a pair. For example, `concordance` and `concordancefit`; the former is the user front end and the latter does the actual work. Other package authors might want to access the lower level interface, while accepting the penalty of fewer error checks.
- Don't mess it up!

This meant preserving the current argument names as much as possible. Appendix A.1 summarizes changes that were made which are not backwards compatible.

The two other major changes are to collapse many of vignettes into this single large one, and the parallel creation of an actual book. Documentation is an ongoing process, and there are still things the package can do which are not well described. That said, we've recognized that the package needs more than a vignette. With the book's (eventual) appearance this vignette can also be more brief, essentially leaving out a lot of the theory.

Version 3 will not appear all at once, however; it will take some time to get all of the documentation sorted out in the way that we like.

1.2 Survival data

The survival package is concerned with time-to-event analysis. Such outcomes arise very often in the analysis of medical data: time from chemotherapy to tumor recurrence, the durability of a joint replacement, recurrent lung infections in subjects with cystic fibrosis, the appearance of hypertension, hyperlipidemia and other comorbidities of age, and of course death itself, from which the overall label of "survival" analysis derives. A key principle of all such studies is that "it takes time to observe time", which in turn leads to two of the primary challenges.

1. Incomplete information. At the time of an analysis, not everyone will have yet had the event. This is a form of partial information known as *censoring*: if a particular subject was enrolled in a study 2 years ago, and has not yet had an event at the time of analysis, we only know that their time to event is > 2 years.
2. Dated results. In order to report 5 year survival, say, from a treatment, patients need to be enrolled and then followed for 5+ years. By the time recruitment and follow-up is finished, analysis done, the report finally published the treatment in question might be 8 years old and considered to be out of date. This leads to a tension between early reporting and long term outcomes.

Survival data is often represented as a pair (t_i, δ_i) where t is the time until endpoint or last follow-up, and δ is a 0/1 variable with 0= "subject was censored at t" and 1 ="subject had an event at t", or in R code as `Surv(time, status)`. The status variable can be logical, e.g., `vtype=='death'` where `vtype` is a variable in the data set. An alternate view is to think of time

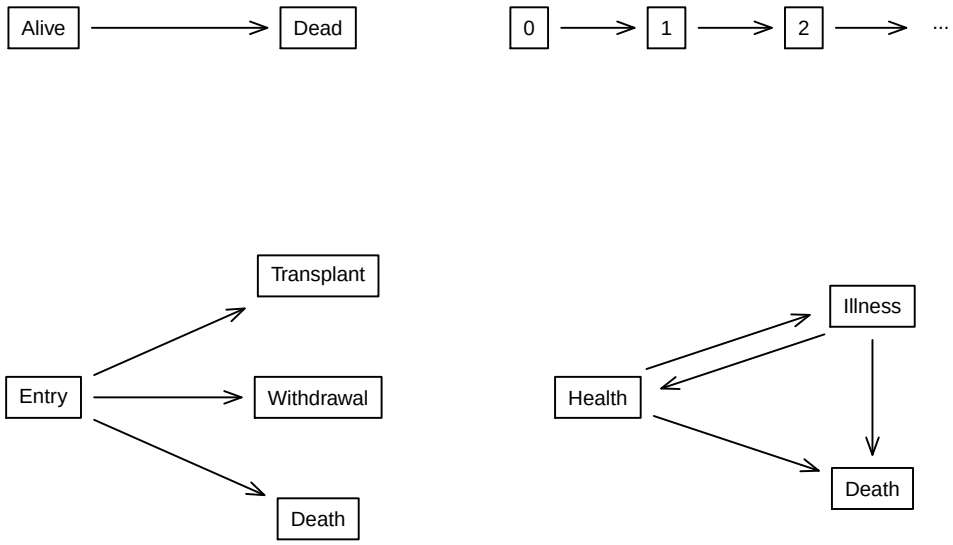


Figure 1.1: Four multiple event models.

to event data as a multi-state process as is shown in figure 1.1. The upper left panel is simple survival with two states of alive and dead, "classic" survival analysis. The other three panels show repeated events of the same type (upper right)

competing risks for subjects on a liver transplant waiting list(lower left) and the illness-death model (lower right). In this approach interest normally centers on the transition rates or hazards (arrows) from state to state (box to box). For simple survival the two multistate/hazard and the time-to-event viewpoints are equivalent, and we will move freely between them, i.e., use whichever viewpoint is handy at the moment. When there more than one transition the rate approach is particularly useful.

The figure also displays a 2 by 2 division of survival data sets, one that will be used to organize other subsections of this document.

	One event per subject	Multiple events per subject
One event type	1	2
Multiple event types	3	4

1.3 Overview

The summary below is purposefully very terse. If you are familiar with survival analysis *and* with other R modeling functions it will provide a good summary. Otherwise, just skim the section to get an overview of the type of computations available from this package, and move on to section 3 for a fuller description.

Surv() A *packaging* function; like I() it doesn't transform its argument. This is used for the left hand side of all the formulas.

- `Surv(time, status)` – right censored data
- `Surv(time, endpoint=='death')` – right censored data, where the status variable is a character or factor
- `Surv(t1, t2, status)` – counting process data
- `Surv(t1, ind, type='left')` – left censoring
- `Surv(time, fstat` – multiple state data, fstat is a factor

aareg Aalen's additive regression model.

- The `timereg` package is a much more comprehensive implementation of the Aalen model, so this document will say little about `aareg`

coxph() Cox's proportional hazards model.

- `coxph(Surv(time, status) ~x, data=aml)` – standard Cox model
- `coxph(Surv(t1, t2, stat) ~ (age + surgery)* transplant)` – time dependent covariates.
- `y <- Surv(t1, t2, stat)`
  `coxph(y ~ strata(inst) * sex + age + treat)` – Stratified model, with a separate baseline per institution, and institution specific effects for sex.

- `coxph(y ~ offset(x1) + x2)` – force in a known term, without estimating a coefficient for it.

cox.zph Computes a test of proportional hazards for the fitted Cox model.

- `zfit <- cox.zph(coxfit); plot(zfit)`

pyears Person-years analysis

survdiff One and k-sample versions of the Fleming-Harrington G^ρ family. Includes the logrank and Gehan-Wilcoxon as special cases.

- `survdiff(Surv(time, status) ~ sex + treat)` – Compare the 4 sub-groups formed by sex and treatment combinations.
- `survdiff(Surv(time, status) ~ offset(pred))` - One-sample test

survexp Predicted survival for an age and sex matched cohort of subjects, given a baseline matrix of known hazard rates for the population. Most often these are US mortality tables, but we have also used local tables for stroke rates.

- `survexp(entry.dt, birth.dt, sex)` – Defaults to US white, average cohort survival
- `pred <- survexp(entry, birth, sex, futime, type='individual')` Data to enter into a one sample test for comparing the given group to a known population.

survfit Fit a survival curve.

- `survfit(Surv(time, status))` – Simple Kaplan-Meier
- `survfit(Surv(time, status) ~ rx + sex)` – Four groups
- `fit <- coxph(Surv(time, stat) ~ rx + sex)`
  `survfit(fit, list(rx=1, sex=2))` – Predict curv

survreg Parametric survival models.

- `survreg(Surv(time, stat) ~ x, dist='loglogistic')` - Fit a log-logistic distribution.

Data set creation

- `survSplit` break a survival data set into disjoint portions of time
- `tmerge` create survival data sets with time-dependent covariates and/or multiple events
- `survcheck` sanity checks for survival data sets

1.4 Mathematical Notation

We start with some mathematical background and notation, simply because it will be used later. A key part of the computations is the notion of a *risk set*. That is, in time to event analysis a given subject will only be under observation for a specified time. Say for instance that we are interested in the patient experience after a certain treatment, then a patient recruited on

March 10 1990 and followed until an analysis date of June 2000 will have 10 years of potential follow-up, but someone who recieved the treatment in 1995 will only have 5 years at the analysis date. Let $Y_i(t)$, $i = 1, \ldots, n$ be the indicator that subject i is at risk and under observation at time t. Let $N_i(t)$ be the step function for the ith subject, which counts the number of "events" for that subject up to time t. There might me things that can happen multiple times such as rehospitalization, or something that only happens once such as death. The total number of events that have occurred up to time t will be $\overline{N}(t) = \sum N_i(t)$, and the number of subjects at risk at time t will be $\overline{Y}(t) = \sum Y_i(t)$. Time-dependent covariates for a subject are the vector $X_i(t)$. It will also be useful to define $d(t)$ as the number of deaths that occur exactly at time t.

Chapter 2

Survival curves

2.1 One event type, one event per subject

The most common depiction of survival data is the Kaplan-Meier curve, which is a product of survival probabilities:

$$\hat{S}_{KM}(t) = \prod_{s<t} \frac{\overline{Y}(ts) - d(s)}{\overline{Y}(s)}\,. \tag{2.1}$$

Graphically, the Kaplan-Meier survival curve appears as a step function with a drop at each death. Censoring times are often marked on the plot as "+" symbols. KM curves are created with the `survfit` function. The left-hand side of the formula will be a Surv object and the right hand side contains one or more categorical variables that will divide the observations into groups. For a single curve use ~ 1 as the right hand side.

```
> fit1 <- survfit(Surv(futime, fustat) ~ resid.ds, data=ovarian)
> print(fit1, rmean= 730)
Call: survfit(formula = Surv(futime, fustat) ~ resid.ds, data = ovarian)

            n events rmean* se(rmean) median 0.95LCL 0.95UCL
resid.ds=1 11      3    666      35.4     NA     638      NA
resid.ds=2 15      9    463      62.1    464     329      NA
    * restricted mean with upper limit =  730
> summary(fit1, times= (0:4)*182.5, scale=365)
Call: survfit(formula = Surv(futime, fustat) ~ resid.ds, data = ovarian)

                resid.ds=1
 time n.risk n.event survival std.err lower 95% CI upper 95% CI
  0.0     11       0    1.000  0.0000        1.000            1
  0.5     11       0    1.000  0.0000        1.000            1
  1.0     10       1    0.909  0.0867        0.754            1
  1.5      8       0    0.909  0.0867        0.754            1
  2.0      6       2    0.682  0.1536        0.438            1
```

```
                resid.ds=2
 time n.risk n.event survival std.err lower 95% CI upper 95% CI
  0.0     15       0    1.000   0.000        1.000        1.000
  0.5     12       3    0.800   0.103        0.621        1.000
  1.0     10       3    0.600   0.126        0.397        0.907
  1.5      4       3    0.375   0.130        0.190        0.738
  2.0      4       0    0.375   0.130        0.190        0.738
```

The default printout is very brief, only one line per curve, showing the number of observations, number of events, median survival, and optionally the restricted mean survival time (RMST) in each of the groups. In the above case we used the value at 2.5 years = 913 days as the upper threshold for the RMST, the value of 453 for females represents an average survival for 453 of the next 913 days after enrollment in the study. The summary function gives a more complete description of the curve, in this case we chose to show the values every 6 months for the first two years. In this case the number of events (`n.event`) column is the number of deaths in the interval between two time points, all other columns reflect the value at the chosen time point.

Arguments for the survfit function include the usual `data`, `weights`, `subset` and `na.action` arguments common to modeling formulas. A further set of arguments have to do with standard errors and confidence intervals, defaults are shown in parenthesis.

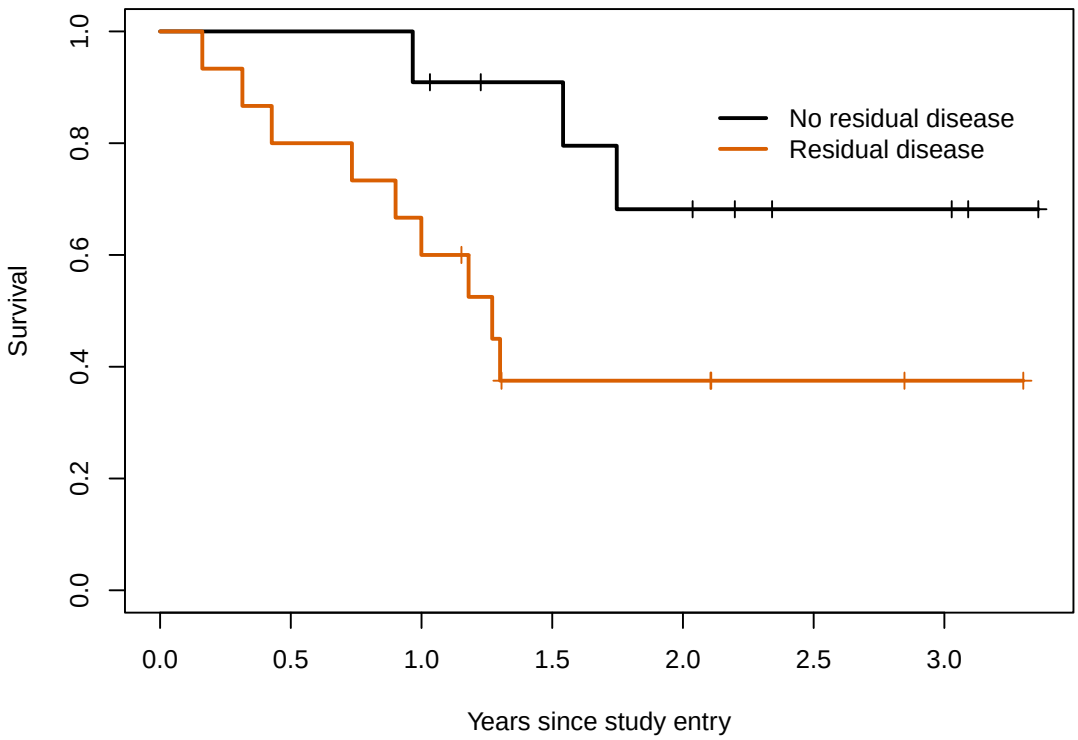
- se.fit (TRUE): compute a standard error of the estimates. In a few rare circumstances omitting the standard error can save computation time.
- conf.int (.95): the level of confidence interval, or FALSE if intervals are not desired.
- conf.type ('log'): transformation to be used in computing the confidence intervals.
- conf.lower ('usual'): optional modification of the lower interval.

For the default `conf.type` the confidence intervals are computed as $\exp[\log(p) \pm 1.96\text{se}(\log(p))]$ rather than the direct formula of $p \pm 1.96(\text{se})(p)$, where $p = S(t)$ is the survival probability. Many authors have investigated the behavior of transformed intervals, and a general conclusion is that the direct intervals do not behave well, particularly near 0 and 1, while all the others are acceptable. Which of the choices of log, log-log, or logit is "best" depends on the details of any particular simulation study, all are available as options in the function. (The default corresponds to the most recent paper the author had read, at the time the default was chosen; a current meta review might give a slight edge to the log-log option.)

The `conf.lower` option is mostly used for graphs. If a study has a long string of censored observations, it is intuitive that the precision of the estimated survival must be decreasing due to a smaller sample size, but the formal standard error will not change until the next death. This option widens the confidence interval between death times, proportional to the number at risk, giving a visual clue of the decrease in n. There is only a small (and decreasing) population of users who make use of this.

The most common use of survival curves is to plot them, as shown below.

```
> plot(fit1, col=1:2, xscale=365.25, lwd=2, mark.time=TRUE,
       xlab="Years since study entry", ylab="Survival")
> legend(750, .9, c("No residual disease", "Residual disease"),
         col=1:2, lwd=2, bty='n')
```



Curves will appear in the plot in the same order as they are listed by `print`; this is a quick way to remind ourselves of which subset maps to each color or linetype in the graph. Curves can also be labeled using the `pch` option to place marks on the curves. The location of the marks is controlled by the `mark.time` option which has a default value of FALSE (no marks). A vector of numeric values specifies the location of the marks, optionally a value of `mark.time=TRUE` will cause a mark to appear at each censoring time; this can result in far too many marks if n is large, however. By default confidence intervals are included on the plot of there is a single curve, and omitted if there is more than one curve.

Other options:

- xaxs('r') It has been traditional to have survival curves touch the left axis (I will not speculate as to why). This can be accomplished using `xaxs='S'`, which was the default before survival 3.x. The current default is the standard R style, which leaves space between the curve and the axis.

- The follow-up time in the data set is in days. This is very common in survival data, since it is often generated by subtracting two dates. The xscale argument has been used to convert to years. Equivalently one could have used `Surv(futime/365.25, status)` in the original

call to convert all output to years. The use of `scale` in print and summary and `xscale` in plot is a historical mistake.

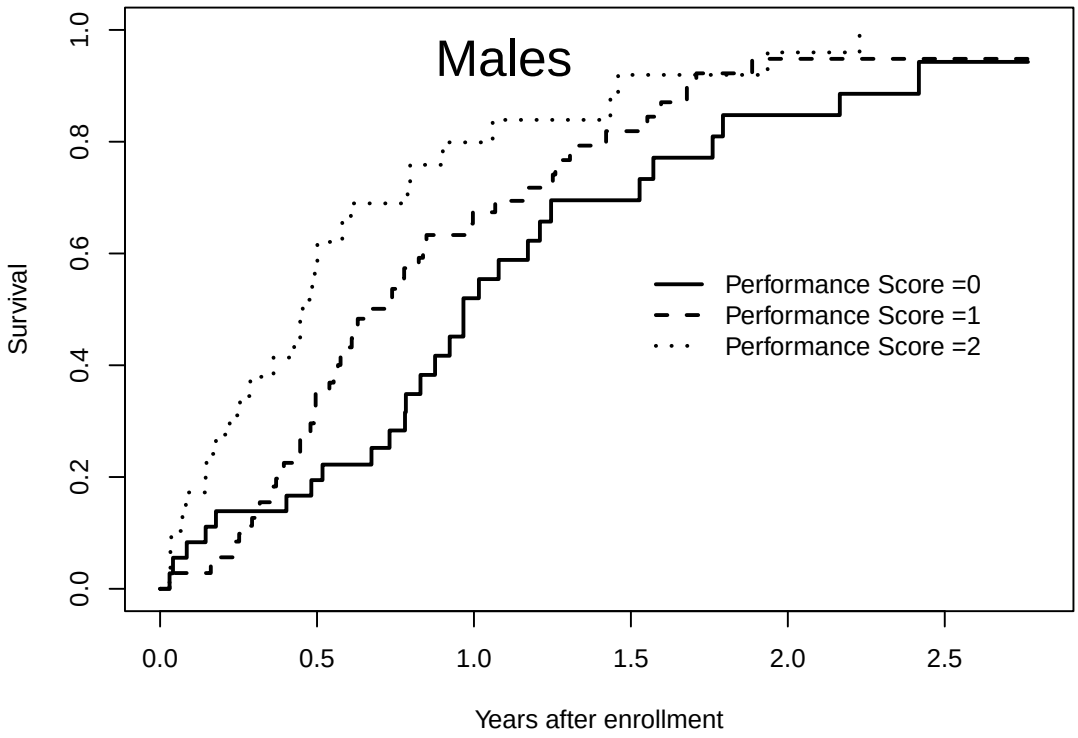
- Subjects who were not followed to death are *censored* at the time of last contact. These appear as + marks on the curve. Use the `mark.time` option to suppress or change the symbol.
- By default pointwise 95% confidence curves will be shown if the plot contains a single curve; they are by default not shown if the plot contains 2 or more groups.
- Confidence intervals are normally created as part of the `survfit` call. However, they can be omitted at that point, and added later by the plot routine.
- There are many more options, see `help('plot.survfit')`.

The result of a `survfit` call can be subscripted. This is useful when one wants to plot only a subset of the curves. Here is an example using a larger data set collected on a set of patients with advanced lung cancer [6], which better shows the impact of the Eastern Cooperative Oncolgy Group (ECOG) score. This is a simple measure of patient mobility:

- 0: Fully active, able to carry on all pre-disease performance without restriction
- 1:Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work
- 2: Ambulatory and capable of all selfcare but unable to carry out any work activities. Up and about more than 50% of waking hours
- 3: Capable of only limited selfcare, confined to bed or chair more than 50% of waking hours
- 4: Completely disabled. Cannot carry on any selfcare. Totally confined to bed or chair

```
> fit2 <- survfit(Surv(time, status) ~  sex + ph.ecog, data=lung)
> fit2
Call: survfit(formula = Surv(time, status) ~ sex + ph.ecog, data = lung)

   1 observation deleted due to missingness
                 n events median 0.95LCL 0.95UCL
sex=1, ph.ecog=0 36     28    353     303     558
sex=1, ph.ecog=1 71     54    239     207     363
sex=1, ph.ecog=2 29     28    166     105     288
sex=1, ph.ecog=3  1      1    118      NA      NA
sex=2, ph.ecog=0 27      9    705     350      NA
sex=2, ph.ecog=1 42     28    450     345     687
sex=2, ph.ecog=2 21     16    239     199     444
```

```
> plot(fit2[1:3], lty=1:3, lwd=2, xscale=365.25, fun='event',
        xlab="Years after enrollment", ylab="Survival")
> legend(550, .6, paste("Performance Score", 0:2, sep=' ='),
        lty=1:3, lwd=2, bty='n')
> text(400, .95, "Males", cex=2)
```



The argument `fun='event'` has caused the death rate $D = 1 - S$ to be plotted. The choice between the two forms is mostly personal, but some areas such as cancer trial always plot survival (downhill) and other such as cardiology prefer the event rate (uphill).

Mean and median For the Kaplan-Meier estimate, the estimated mean survival is undefined if the last observation is censored. One solution, used here, is to redefine the estimate to be zero beyond the last observation. This gives an estimated mean that is biased towards zero, but there are no compelling alternatives that do better. With this definition, the mean is estimated as

$$\hat{\mu} = \int_0^T \hat{S}(t)dt$$

where $\hat{S}$ is the Kaplan-Meier estimate and T is the maximum observed follow-up time in the study. The variance of the mean is

$$\text{var}(\hat{\mu}) = \int_0^T \left(\int_t^T \hat{S}(u)du \right)^2 \frac{d\overline{N}(t)}{\overline{Y}(t)(\overline{Y}(t) - \overline{N}(t))}$$

where $\bar{N} = \sum N_i$ is the total counting process and $\bar{Y} = \sum Y_i$ is the number at risk.

The sample median is defined as the first time at which $\hat{S}(t) \leq .5$. Upper and lower confidence intervals for the median are defined in terms of the confidence intervals for S: the upper confidence interval is the first time at which the upper confidence interval for $\hat{S}$ is $\leq .5$. This corresponds to drawing a horizontal line at 0.5 on the graph of the survival curve, and using intersections of this line with the curve and its upper and lower confidence bands. In the very rare circumstance that the survival curve has a horizontal portion at exactly 0.5 (e.g., an even number of subjects and no censoring before the median) then the average time of that horizonal segment is used. This agrees with usual definition of the median for even n in uncensored data.

2.2 Repeated events

This is the case of a single event type, with the possibility of multiple events per subject. Repeated events are quite common in industrial reliability data. As an example, consider a data set on the replacement times of diesel engine valve seats. The simple data set `valveSeats` contains an engine identifier, time, and a status of 1 for a replacement and 0 for the end of the inspection interval for that engine; the data is sorted by time within engine. To accommodate multiple events for an engine we need to rewrite the data in terms of time intervals. For instance, engine 392 had repairs on days 258 and 328 and a total observation time of 377 days, and will be represented as three intervals of (0, 258), (258, 328) and (328, 377) thus:

```
   id time1 time2 status
1 392     0   258      1
2 392   258   328      1
3 392   328   377      0
```

Intervals of length 0 are illegal for `Surv` objects. There are 3 engines that had 2 valves repaired on the same day, which will create such an interval. To work around this move the first repair back in time by a tiny amount.

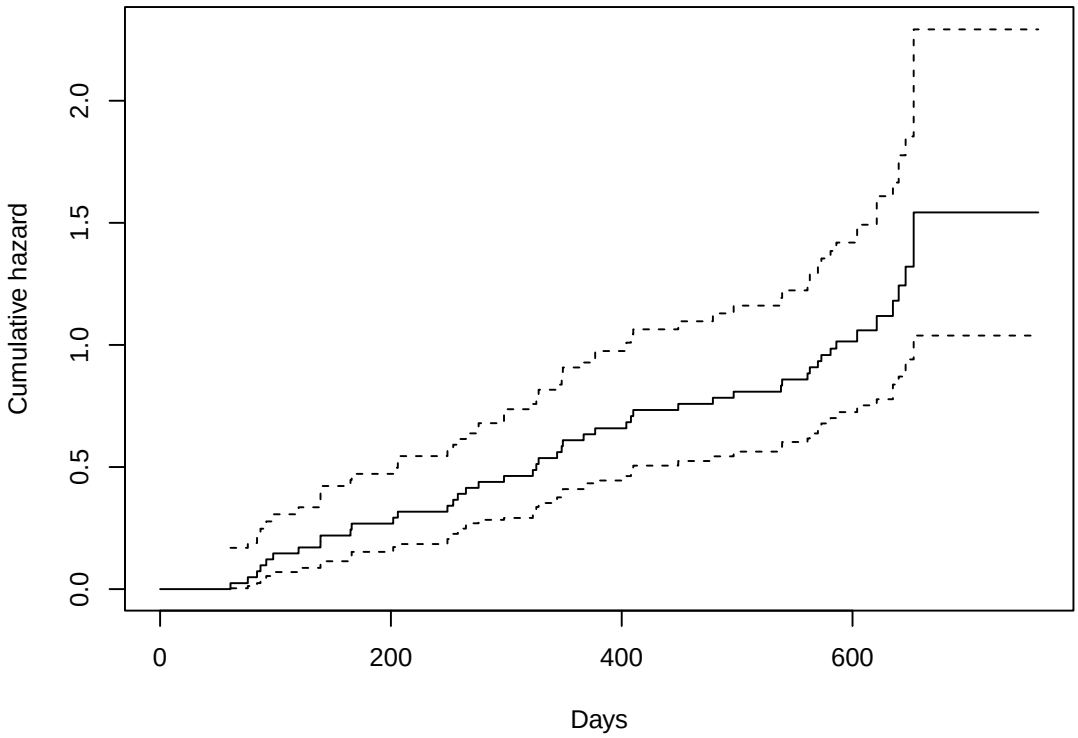
```
> vdata <- with(valveSeat, data.frame(id=id, time2=time, status=status))
> first <- !duplicated(vdata$id)
> vdata$time1 <- ifelse(first, 0,  c(0, vdata$time[-nrow(vdata)]))
> double <- which(vdata$time1 == vdata$time2)
> vdata$time1[double] <- vdata$time1[double] -.01
> vdata$time2[double-1] <- vdata$time1[double]
> vdata[1:7, c("id", "time1", "time2", "status")]
   id  time1  time2 status
1 251   0.00 761.00      0
2 252   0.00 759.00      0
3 327   0.00  98.00      1
4 327  98.00 667.00      0
5 328   0.00 326.00      1
6 328 326.00 652.99      1
7 328 652.99 653.00      1
> survcheck(Surv(time1, time2, status) ~ 1, id=id, data=vdata)
```

```
Call:
survcheck(formula = Surv(time1, time2, status) ~ 1, data = vdata,
    id = id)

Unique identifiers       Observations        Transitions
                41                 89                 48

Transitions table:
      to
from    1 (censored)
  (s0) 24         17
  1    24         24

Number of subjects with 0, 1, ... transitions to each state:
       count
state    0 1 2 3 4
  1     17 9 8 5 2
  (any) 17 9 8 5 2
```

Creation of (start time, end time) intervals is a common data manipulation task when there are multiple events per subject. A later chapter will discuss the `tmerge` function, which is very often useful for this task. The `survcheck` function can be used as check for some of more common errors that arise in creation; it also will be covered in more detail in a later section. (The output will be also be less cryptic for later cases, where the states have been labeled.) In the above data, the engines could only participate in 2 kinds of transitions: from an unnamed initial state to a repair, (s0) $\rightarrow$ 1, or from one repair to another one, 1 $\rightarrow$ 1, or reach end of follow-up. The second table printed by `survcheck` tells us that 17 engines had 0 transitions to state 1, i.e., no valve repairs before the end of observation for that engine, 9 had 1 repair, etc. Perhaps the most important message is that there were no warnings about suspicious data.

We can now compute the survival estimate. When there are multiple observations per subject the `id` statement is necessary. (It is a good idea any time there *could* be multiples, even if there are none, as it lets the underlying routines check for doubles.)

```
> vfit <- survfit(Surv(time1, time2, status) ~1, data=vdata, id=id)
> plot(vfit, cumhaz=TRUE, xlab="Days", ylab="Cumulative hazard")
```



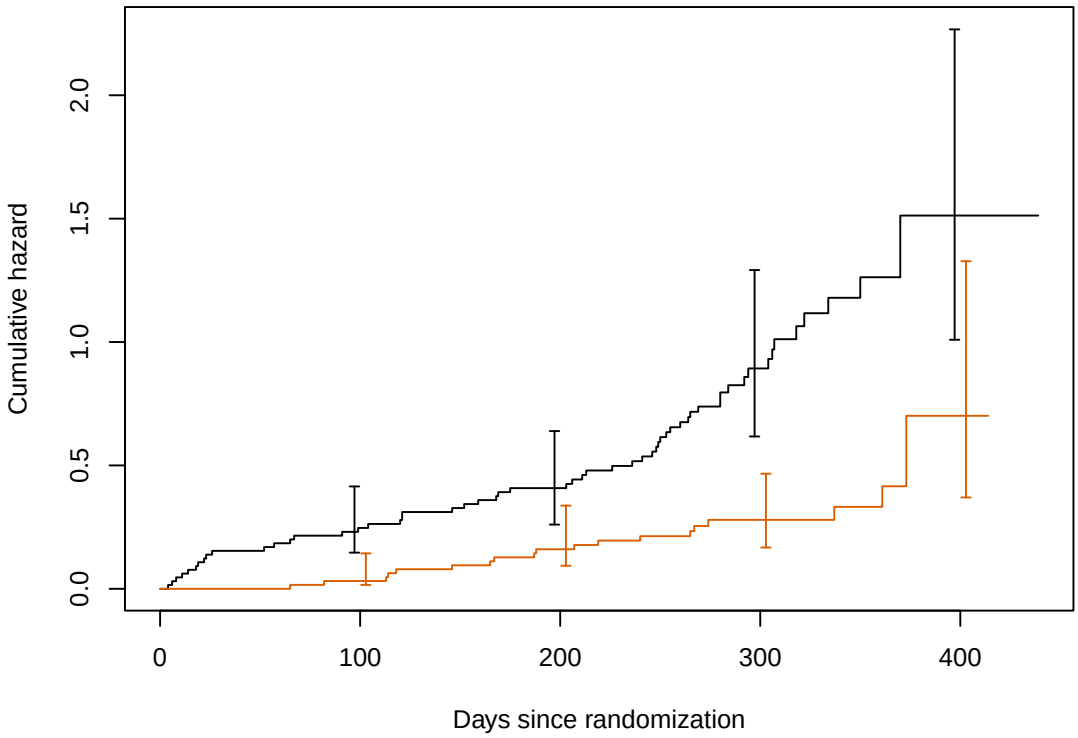
By default, the `survfit` routine computes both the survival and the Nelson cumulative hazard estimate

$$\hat{\Lambda}(t) = \sum_{i-1}^{n} \int_0^t \frac{dN_i(s)}{\overline{Y}(s)}$$

Like the KM, the Nelson estimate is a step function, it starts at zero and has a step of size $d(t)/\overline{Y}(t)$ at each death. To plot the cumulative hazard the `cumhaz` argument of `survfit` is used. In multi-event data, the cumulative hazard is an estimate of the expected *number* of events for a unit that has been observed for the given amount of time, whereas the survival S estimates the probability that a unit has had 0 repairs. The cumulative hazard is the more natural quantity to plot in such studies; in reliability analysis it is also known as the *mean cumulative function*.

The estimate is also important in multi-state models. An example is the occurene of repeated infections in children with chronic granultomous disease, as found in the `cgd` data set.

```
> cgdsurv <- survfit(Surv(tstart, tstop, status) ~ treat, cgd, id=id)
> plot(cgdsurv, cumhaz=TRUE, col=1:2, conf.times=c(100, 200, 300, 400),
       xlab="Days since randomization", ylab="Cumulative hazard")
```



2.3 Competing risks

The case of multiple event types, but only one event per subject is commonly known as competing risks. We do not need the (time1, time2) data form for this case, since each subject has only a single outcome, but we do need a way to identify different outcomes. In the prior sections, `status` was either a logical or 0/1 numeric variable that represents censoring (0 or FALSE) or an event (1 or TRUE), and the result of `survfit` was a single survival curve for each group. For competing risks data `status` will be a factor; the first level of the factor is used to code censoring while the remaining ones are possible outcomes.

2.3.1 Simple example

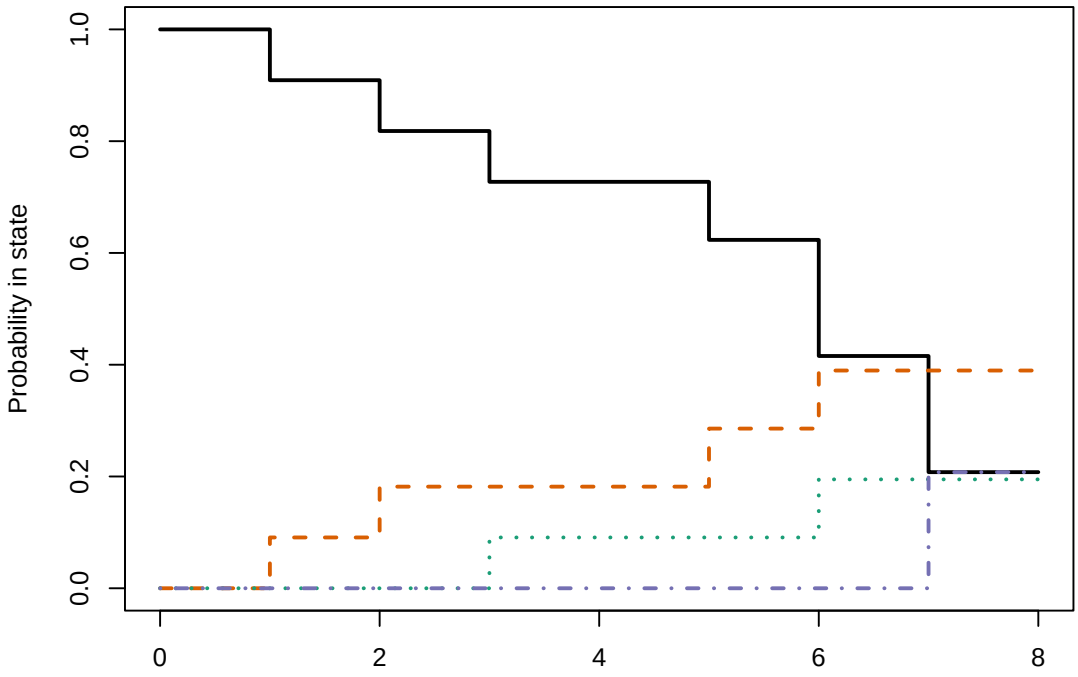
Here is a simple competing risks example where the three endpoints are labeled as a, b and c.

```
> crdata <- data.frame(time= c(1:8, 6:8),
                       endpoint=factor(c(1,1,2,0,1,1,3,0,2,3,0),
                                       labels=c("censor", "a", "b", "c")),
                       istate=rep("entry", 11),
                       id= LETTERS[1:11])
> tfit  <- survfit(Surv(time, endpoint) ~ 1, data=crdata, id=id, istate=istate)
> dim(tfit)
```

```
states
     4
> summary(tfit)
Call: survfit(formula = Surv(time, endpoint) ~ 1, data = crdata, id = id,
    istate = istate)

 time n.risk n.event Pr(entry)  Pr(a)  Pr(b) Pr(c)
    1     11       1     0.909 0.0909 0.0000 0.000
    2     10       1     0.818 0.1818 0.0000 0.000
    3      9       1     0.727 0.1818 0.0909 0.000
    5      7       1     0.623 0.2857 0.0909 0.000
    6      6       2     0.416 0.3896 0.1948 0.000
    7      4       2     0.208 0.3896 0.1948 0.208
```

The resulting object `tfit` contains an estimate of P(state), the probability of being in each state at each time t. P is a matrix with one row for each time and one column for each of the four states a–c and "still in the starting state". By definition each row of P sums to 1. We will also use the notation $p(t)$ where p is a vector with one element per state and $p_j(t)$ is the fraction in state j at time t. The plot below shows all 4 curves. (Since they sum to 1 one of the 4 curves is redundant, often the entry state is omitted since it is the least interesting.) In the `plot.survfit` function there is the argument `noplot="(s0)"` which indicates that curves for state (s0) will not be plotted. If we had not specified `istate` in the call to `survfit`, the default label for the initial state would have been "s0" and t he solid curve would not have been plotted.

```
> plot(tfit, col=1:4, lty=1:4, lwd=2, ylab="Probability in state")
```



The resulting `survfms` object appears as a matrix and can be subscripted as such, with a column for each state and rows for each group, each unique combination of values on the right hand side of the formula is a group or strata. This makes it simple to display a subset of the curves using plot or lines commands. The entry state in the above fit, for instance, can be displayed with `plot(tfit[,1])`.

```
> dim(tfit)
states
     4
> tfit$states
[1] "entry" "a"     "b"     "c"
```

The curves are computed using the Aalen-Johansen estimator. This is an important concept, and so we work it out below.

1. The starting point is the column vector $p(0) = (1, 0, 0, 0)$, everyone starts in the first state.
2. At time 1, the first event time, form the 4 by 4 transition matrix T_1

$$T(1) = \begin{pmatrix} 10/11 & 1/11 & 0/11 & 0/11 \\ 0 & 1 & 0 & 0 \\ 0 & 0 & 1 & 0 \\ 0 & 0 & 0 & 1 \end{pmatrix} p(1) \qquad = p(0)T_1$$

The first row of $T(1)$ describes the disposition of everyone who is in state 1 and under observation at time 1: 10/11 stay in state 1 and 1 subject transitions to state a. There is no

one in the other 3 states, so rows 2–4 are technically undefined; use a default "stay in the same state" row which has 1 on the diagonal. (Since no one ever leaves states a, b, or c, the bottom three rows of T will continue to have this form.)

3. At time 2 the first row will be (9/10, 0, 1/10, 0), and $p(2) = p(1)T(2) = p(0)T(1)T(2)$.

Continue this until the last event time. At a time point with only censoring, such as time 4, T would be the identity matrix.

It is straightforward to show that when there are only two states of alive -> dead, then $p_1(t)$ replicates the Kaplan-Meier computation. For competing risks data such as the simple example above, $p(t)$ replicates the cumulative incidence (CI) estimator. That is, both the KM and CI are both special cases of the Aalen-Johansen. The AJ is more general, however; a given subject can have multiple transitions from state to state, including transitions to a state that was visited earlier.

2.3.2 Monoclonal gammopathy

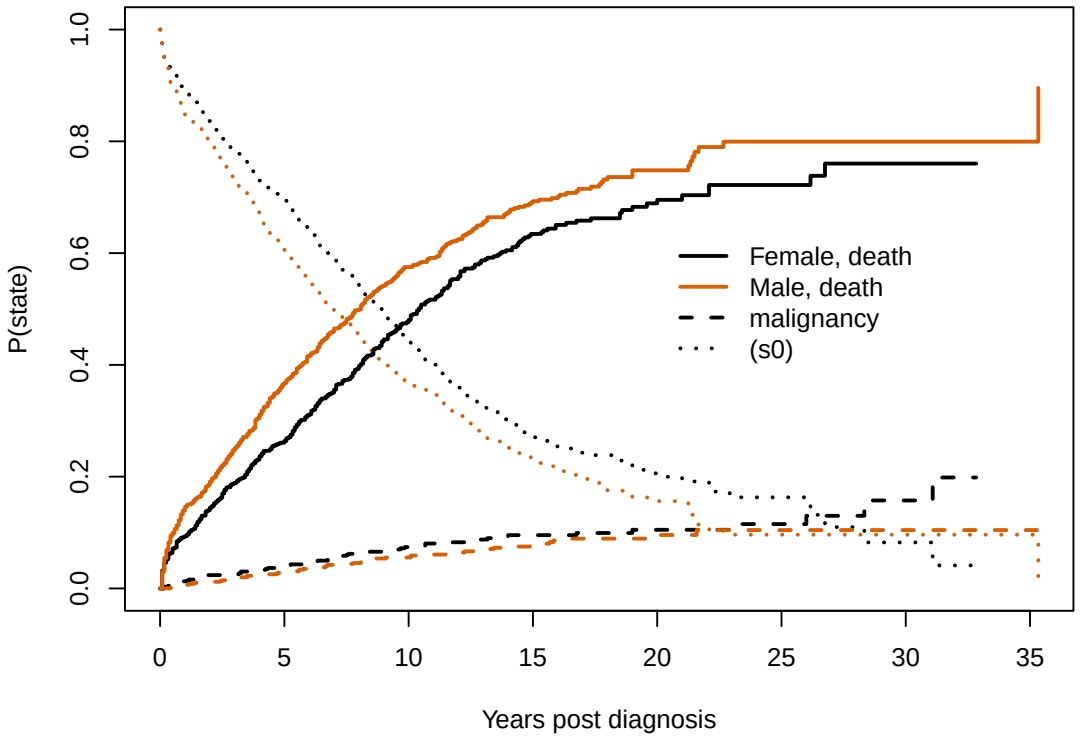
The `mgus2` data set contains information of 1384 subjects who were who were found to have a particular pattern on a laboratory test (monoclonal gammopathy of undetermined significance or MGUS). The genesis of the study was a suspicion that such a result might indicate a predisposition to plasma cell malignancies such a multiple myeloma; subjects were followed forward to assess whether an excess did occur. The mean age at diagnosis is 63 years, so death from other causes will be an important competing risk. Here are a few observations of the data set, one of which experienced progression to a plasma cell malignancy.

```
> mgus2[55:59, -(4:7)]
   id age sex ptime pstat futime death etime event
55 55  82   F    94     0     94     1    94 death
56 56  78   M    29     1     44     1    29   pcm
57 57  79   F    84     0     84     1    84 death
58 58  72   F   321     0    321     1   321 death
59 59  80   F   147     0    147     1   147 death
```

To generate competing risk curves create a new (etime, event) pair. Since each subject has at most 1 transition, we do not need a multi-line (time1, time2) dataset.

```
> event <- with(mgus2, ifelse(pstat==1, 1, 2*death))
> event <- factor(event, 0:2, c("censored", "progression", "death"))
> etime <- with(mgus2, ifelse(pstat==1, ptime, futime))
> crfit <- survfit(Surv(etime, event) ~ sex, mgus2)
> crfit
Call: survfit(formula = Surv(etime, event) ~ sex, data = mgus2)

               n nevent    rmean*
sex=F, (s0)  631      0 139.01247
sex=M, (s0)  753      0 122.97693
sex=F, pcm   631     59  42.77078
sex=M, pcm   753     56  31.82962
```

```
sex=F, death 631    370 242.21675
sex=M, death 753    490 269.19344
   *restricted mean time in state (max time = 424 )
> plot(crfit, col=1:2,  noplot="",
       lty=c(3,3,2,2,1,1), lwd=2, xscale=12,
       xlab="Years post diagnosis", ylab="P(state)")
> legend(240, .65, c("Female, death", "Male, death", "malignancy", "(s0)"),
        lty=c(1,1,2,3), col=c(1,2,1,1), bty='n', lwd=2)
```

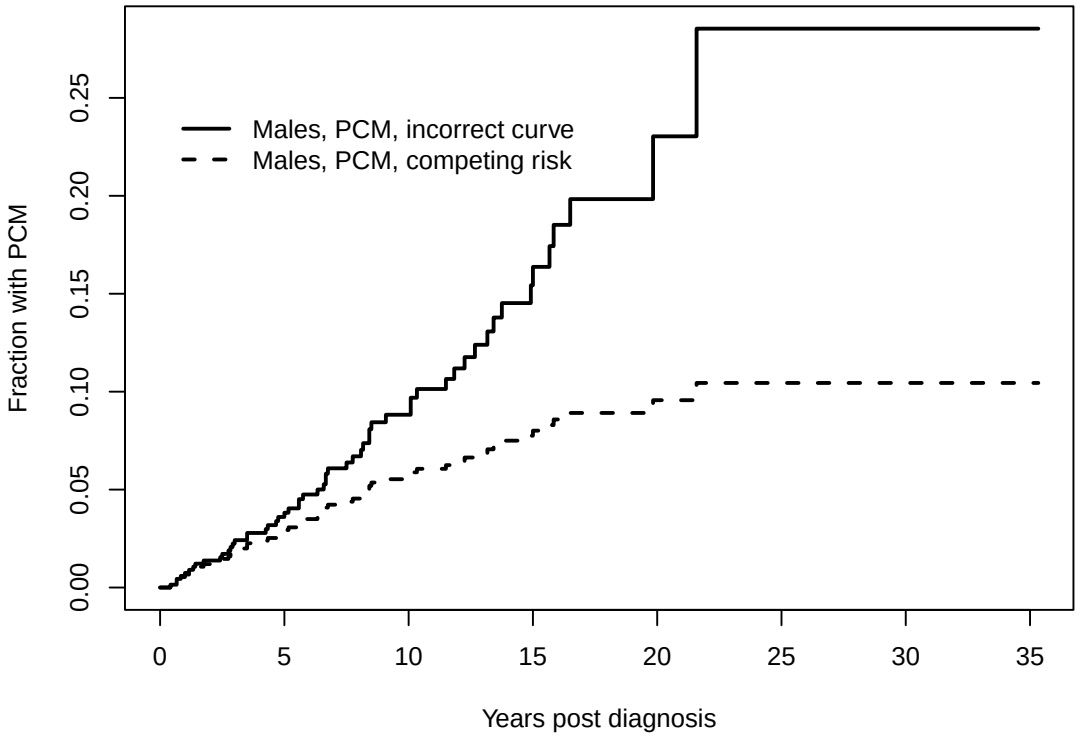


There are 3 curves for females, one for each of the three states, and 3 for males. The three curves sum to 1 at any given time (everyone has to be somewhere), and the default action for `plot.survfit` is to leave out the "still in original state" curve (s0) since it is usually the least interesting, but in this case we have shown all 3. We will return to this example when exploring models.

A common mistake with competing risks is to use the Kaplan-Meier separately on each event type while treating other event types as censored. The next plot is an example of this for the PCM endpoint.

```
> pcmbad <- survfit(Surv(etime, pstat) ~ sex, data=mgus2)
> plot(pcmbad[2], mark.time=FALSE, lwd=2, fun="event", conf.int=FALSE, xscale=12,
       xlab="Years post diagnosis", ylab="Fraction with PCM")
> lines(crfit[2,2], lty=2, lwd=2, mark.time=FALSE, conf.int=FALSE)
```

```
> legend(0, .25, c("Males, PCM, incorrect curve", "Males, PCM, competing risk"),
        col=1, lwd=2, lty=c(1,2), bty='n')
```



There are two problems with the `pcmbad` fit. The first is that it attempts to estimate the expected occurrence of plasma cell malignancy (PCM) if all other causes of death were to be disallowed. In this hypothetical world it is indeed true that many more subjects would progress to PCM (the incorrect curve is higher), but it is also not a world that any of us will ever inhabit. This author views the result in much the same light as a discussion of survival after the zombie apocalypse. The second problem is that the computation for this hypothetical case is only correct if all of the competing endpoints are independent, a situation which is almost never true. We thus have an unreliable estimate of an uninteresting quantity. The competing risks curve, on the other hand, estimates the fraction of MGUS subjects who *will experience* PCM, a quantity sometimes known as the lifetime risk, and one which is actually observable.

The last example chose to plot only a subset of the curves, something that is often desirable in competing risks problems to avoid a "tangle of yarn" plot that simply has too many elements. This is done by subscripting the `survfit` object. For subscripting, multi-state curves behave as a matrix with the outcomes as the second subscript. The columns are in order of the levels of `event`, i.e., as displayed by our earlier call to `table(event)`. The first subscript indexes the groups formed by the right hand side of the model formula, and will be in the same order as simple survival curves. Thus `mfit2[2,2]` corresponds to males (2) and the PCM endpoint (2). Curves are listed and plotted in the usual matrix order of R.

```
> dim(crfit)
```

```
strata states
     2      3
> crfit$strata
sex=F sex=M
  227   227
> crfit$states
[1] "(s0)"  "pcm"   "death"
```

One surprising aspect of multi-state data is that hazards can be estimated independently although probabilities cannot. If you look at the cumulative hazard estimate from the `pcmbad` fit above using, for instance, `plot(pcmbac, cumhaz=TRUE)` you will find that it is identical to the cumulative hazard estimate from the joint fit. This will arise again with Cox models.

2.4 Multi-state data

The most general multi-state data will have multiple outcomes and multiple endpoints per subject. In this case, we will need to use the (time1, time2) form for each subject. The dataset structure is similar to that for time varying covariates in a Cox model: the time variable will be intervals $(t_1, t_2]$ which are open on the left and closed on the right, and a given subject will have multiple lines of data. But instead of covariates changing from line to line, in this case the status variable changes; it contains the state that was entered at time t_2. There are a few restrictions.

- An identifier variable is needed to indicate which rows of the dataframe belong to each subject. If the `id` argument is missing, the code assumes that each row of data is a separate subject, which leads to a nonsense estimate when there are actually multiple rows per subject.
- Subjects do not have to enter at time 0 or all at the same time, but each must traverse a connected segment of time. Disjoint intervals such as the pair $(0, 5]$, $(8, 10]$ are illegal.
- A subject cannot change groups. Any covariates on the right hand side of the formula must remain constant within subject. (This function is not a way to create supposed 'time-dependent' survival curves.)
- Subjects may have case weights, and these weights may change over time for a subject.

The `istate` argument can be used to designate a subject's state at the start of each t_1, t_2 time interval. Like variables in the formula, it is searched for in the `data` argument. If it is not present, every subject is assumed to start in a common entry state which is given the name "(s0)". The parentheses are an echo of "(Intercept)" in a linear model and show a label that was provided by the program rather than the data. The distribution of states just prior to the first event time is treated as the initial distribution of states. In common with ordinary survival, any observation which is censored before the first event time has no impact on the results.

2.4.1 Myeloid data

The `myeloid` data set contains data from a clinical trial in subjects with acute myeloid leukemia. To protect patient confidentiality the data set in the survival package has been slightly perturbed, but results are essentially unchanged. In this comparison of two conditioning regimens, the canonical path for a subject is initial therapy $\rightarrow$ complete response (CR) $\rightarrow$ hematologic stem cell transplant (SCT) $\rightarrow$ sustained remission, followed by relapse or death. Not everyone follows this ideal path, of course.

```
> myeloid[1:5,]
  id trt sex futime death txtime crtime rltime
1  1   B   f    235     1     NA     44    113
2  2   A   m    286     1    200     NA     NA
3  3   A   f   1983     0     NA     38     NA
4  4   B   f   2137     0    245     25     NA
5  5   B   f    326     1    112     56    200
```

The first few rows of data are shown above. The data set contains the follow-up time and status at last follow-up for each subject, along with the time to transplant (txtime), complete response (crtime) or relapse after CR (rltime). Subject 1 did not receive a transplant, as shown by the NA value, and subject 2 did not achieve CR.

Overall survival curves for the data are shown in figure 2.1. The difference between the treatment arms A and B is substantial. A goal of this analysis is to better understand this difference. Code to generate the two curves is below.

```
> sfit0 <- survfit(Surv(futime, death) ~ trt, myeloid)
> plot(sfit0, xscale=365.25, xaxs='r', col=1:2, lwd=2,
       xlab="Years post enrollment", ylab="Survival")
> legend(20, .4, c("Arm A", "Arm B"),
         col=1:2, lwd=2, bty='n')
```

The full multi-state data set can be created with the `tmerge` routine.

```
> mdata <- tmerge(myeloid[,1:2], myeloid,  id=id,  death= event(futime, death),
                  sct = event(txtime), cr = event(crtime),
                  relapse = event(rltime))
> temp <- with(mdata, cr + 2*sct  + 4*relapse + 8*death)
> table(temp)
temp
  0   1   2   3   4   8
325 453 363   1 226 320
```

Our check shows that there is one subject who had CR and stem cell transplant on the same day (temp=3). To avoid length 0 intervals, we break the tie so that complete response (CR) happens first. (Students may be surprised to see anomalies like this, since they never appear in textbook data sets. In real data such issues always appear.)

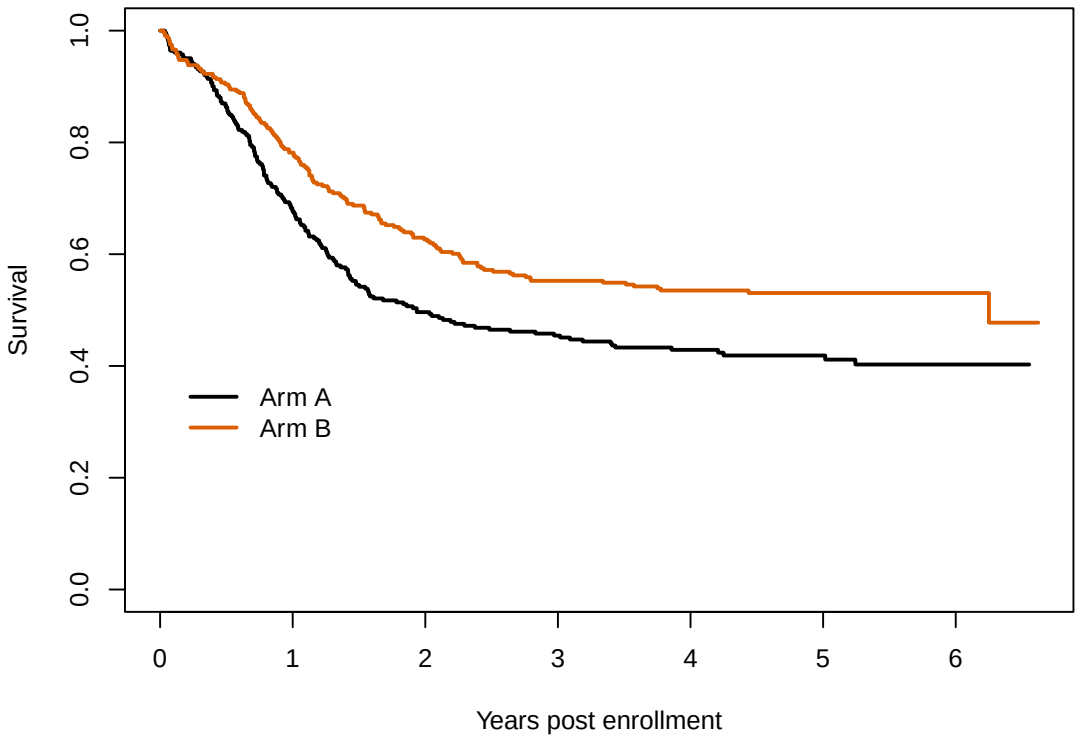


Figure 2.1: Overall survival curves for the two treatments.

```
> tdata <- myeloid  # temporary working copy
> tied <- with(tdata, (!is.na(crtime) & !is.na(txtime) & crtime==txtime))
> tdata$crtime[tied] <- tdata$crtime[tied] -1
> mdata <- tmerge(tdata[,1:2], tdata,  id=id,  death= event(futime, death),
                  sct = event(txtime), cr = event(crtime),
                  relapse = event(rltime),
                  priorcr = tdc(crtime), priortx = tdc(txtime))
> temp <- with(mdata, cr + 2*sct  + 4*relapse + 8*death)
> table(temp)
temp
  0   1   2   4   8
325 454 364 226 320
> mdata$event <- factor(temp, c(0,1,2,4,8),
                        c("none", "CR", "SCT", "relapse", "death"))
> mdata[1:7, c("id", "trt", "tstart", "tstop", "event", "priorcr", "priortx")]
  id trt tstart tstop   event priorcr priortx
1  1   B      0    44      CR       0       0
2  1   B     44   113 relapse       1       0
3  1   B    113   235   death       1       0
4  2   A      0   200     SCT       0       0
5  2   A    200   286   death       0       1
6  3   A      0    38      CR       0       0
7  3   A     38  1983    none       1       0
```

Subject 1 has a CR on day 44, relapse on day 113, death on day 235 and did not receive a stem cell transplant. The data for the first three subjects looks good. Check it out a little more thoroughly using survcheck.

```
> survcheck(Surv(tstart, tstop, event) ~1, mdata, id=id)
Call:
survcheck(formula = Surv(tstart, tstop, event) ~ 1, data = mdata,
    id = id)

Unique identifiers       Observations        Transitions
               646               1689               1364

Transitions table:
         to
from       CR SCT relapse death (censored)
  (s0)    443 106      13    55         29
  CR        0 159     168    17        110
  SCT      11   0      45   149        158
  relapse   0  99       0    99         28
  death     0   0       0     0          0

Number of subjects with 0, 1, ... transitions to each state:
```

```
         count
state       0   1   2   3  4
  CR      192 454   0   0  0
  SCT     282 364   0   0  0
  relapse 420 226   0   0  0
  death   326 320   0   0  0
  (any)    29 201 174 153 89
```

The second table shows that no single subject had more than one CR, SCT, relapse, or death; the intention of the study was to count only the first of each of these, so this is as expected. Several subjects visited all four intermediate states. The transitions table shows 11 subjects who achieved CR *after* stem cell transplant and another 106 who received a transplant before achieving CR, both of which are deviations from the "ideal" pathway. No subjects went from death to another state (which is good).

For investigating the data we would like to add a set of alternate endpoints.

1. The competing risk of CR and death, ignoring other states. This is used to estimate the fraction who ever achieved a complete response.
2. The competing risk of SCT and death, ignoring other states.
3. An endpoint that distinguishes death after SCT from death before SCT.

Each of these can be accomplished by adding further outcome variables to the data set, we do not need to change the time intervals.

```
> levels(mdata$event)
[1] "none"    "CR"      "SCT"     "relapse" "death"
> temp1        <- with(mdata, ifelse(priorcr, 0, c(0,1,0,0,2)[event]))
> mdata$crstat <- factor(temp1, 0:2, c("none", "CR", "death"))
> temp2        <- with(mdata, ifelse(priortx, 0, c(0,0,1,0,2)[event]))
> mdata$txstat <- factor(temp2, 0:2, c("censor", "SCT", "death"))
> temp3     <- with(mdata, c(0,0,1,0,2)[event] + priortx)
> mdata$tx2 <- factor(temp3, 0:3,
                      c("censor", "SCT", "death w/o SCT", "death after SCT"))
```

Notice the use of the `priorcr` variable in defining `crstat`. This outcome variable treats complete response as a terminal state, which in turn means that no further transitions are allowed after reaching CR.

This data set is the basis for our first set of curves, which are shown in figure 2.2. The plot overlays three separate `survfit` calls: standard survival until death, complete response with death as a competing risk, and transplant with death as a competing risk. For each fit we have shown one selected state: the fraction who have died, fraction ever in CR, and fraction ever to receive transplant, respectively. Most of the CR events happen before 2 months (the green vertical line) and nearly all the additional CRs conferred by treatment B occur between months 2 and 8. Most transplants happen after 2 months, which is consistent with the clinical guide of transplant after CR. The survival advantage for treatment B begins between 4 and 6 months, which argues that it could be at least partially a consequence of the additional CR events.

The code to draw figure 2.2 is below. It can be separated into 5 parts:

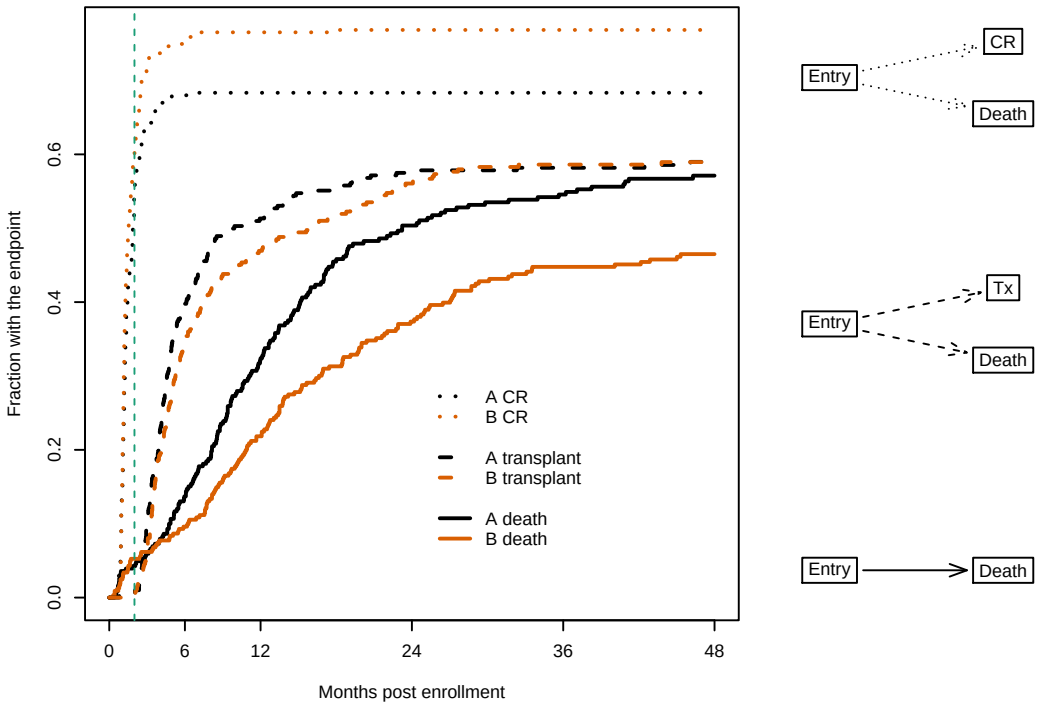


Figure 2.2: Overall survival curves: time to death, to transplant (Tx), and to complete response (CR). Each shows the estimated fraction of subjects who have ever reached the given state. The vertical line at 2 months is for reference. The curves were limited to the first 48 months to more clearly show early events. The right hand panel shows the state-space model for each pair of curves.

1. Fits for the 3 endpoints are simple and found in the first set of lines. The `crstat` and `txstat` variables are factors, which causes multi-state curves to be generated.

2. The `layout` and `par` commands are used to create a multi-part plot with curves on the left and state space diagrams on the right, and to reduce the amount of white space between them.

3. Draw a subset of the curves via subscripting. A multi-state survfit object appears to the user as a matrix of curves, with one row for each group (treatment) and one column for each state. The CR state is the second column in `sfit2`, for instance. The CR fit was drawn first simply because it has the greatest y-axis range, then the other curves added using the lines command.

4. Decoration of the plots. This includes the line types, colors, legend, choice of x-axis labels, etc.

5. Add the state space diagrams. The functions for this are described elsewhere in the vignette.

```
> # I want to have the plots in months, it is simpler to fix time
> #  once rather than repeat xscale many times
> tdata$futime <- tdata$futime * 12 /365.25
> mdata$tstart <- mdata$tstart * 12 /365.25
> mdata$tstop  <- mdata$tstop * 12 /365.25
> sfit1 <- survfit(Surv(futime, death)  ~ trt, tdata) # survival
> sfit2 <- survfit(Surv(tstart, tstop, crstat) ~ trt,
                   data= mdata, id = id) # CR
> sfit3 <- survfit(Surv(tstart, tstop, txstat) ~ trt,
                   data= mdata, id =id) # SCT
> layout(matrix(c(1,1,1,2,3,4), 3,2), widths=2:1)
> oldpar <- par(mar=c(5.1, 4.1, 1.1, .1))
> mlim   <- c(0, 48) # and only show the first 4 years
> plot(sfit2[,"CR"], xlim=mlim,
           lty=3, lwd=2, col=1:2, xaxt='n',
       xlab="Months post enrollment", ylab="Fraction with the endpoint")
> lines(sfit1, mark.time=FALSE, xlim=mlim,
        fun='event', col=1:2, lwd=2)
> lines(sfit3[,"SCT"], xlim=mlim, col=1:2,
            lty=2, lwd=2)
> xtime <- c(0, 6, 12, 24, 36, 48)
> axis(1, xtime, xtime) #axis marks every year rather than 10 months
> temp <- outer(c("A", "B"), c("CR", "transplant", "death"),  paste)
> temp[7] <- ""
> legend(25, .3, temp[c(1,2,7,3,4,7,5,6,7)], lty=c(3,3,3, 2,2,2 ,1,1,1),
         col=c(1,2,0), bty='n', lwd=2)
> abline(v=2, lty=2, col=3)
> # add the state space diagrams
```

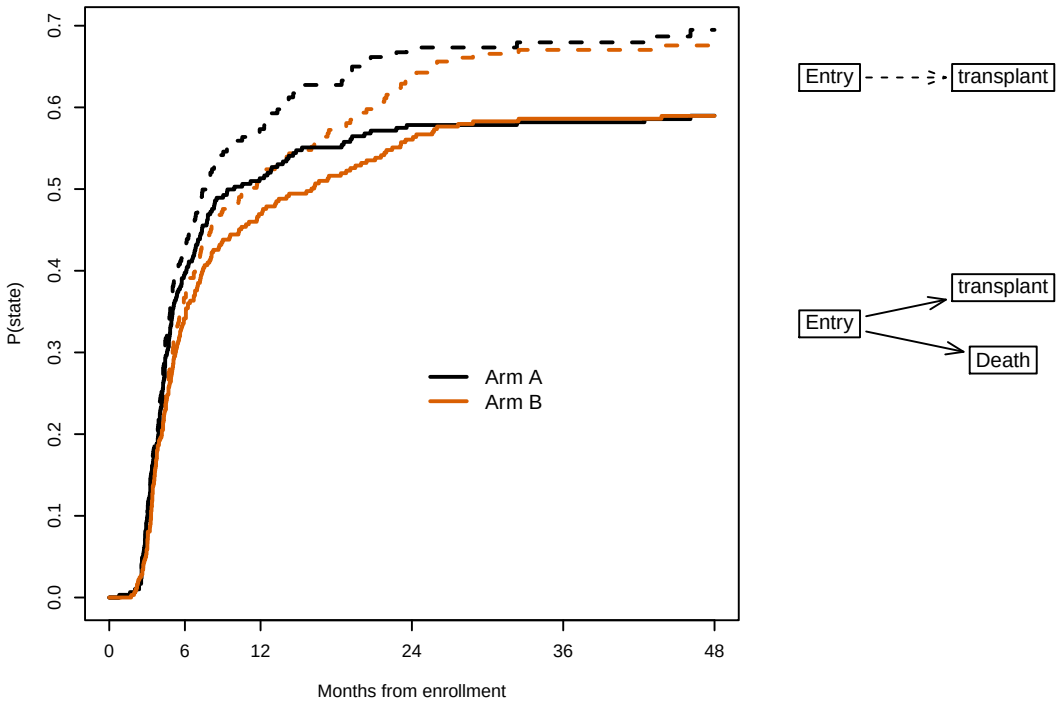


Figure 2.3: Correct (solid) and invalid (dashed) estimates of the number of subjects transplanted.

```
> par(mar=c(4,.1,1,1))
> crisk(c("Entry", "CR", "Death"), alty=3)
> crisk(c("Entry", "Tx", "Death"), alty=2)
> crisk(c("Entry","Death"))
> par(oldpar)
> layout(1)
```

The association between a particular curve and its corresponding state space diagram is critical. As we will see below, many different models are possible and it is easy to get confused. Attachment of a diagram directly to each curve, as was done above, will not necessarily be day-to-day practice, but the state space should always be foremost. If nothing else, draw it on a scrap of paper and tape it to the side of the terminal when creating a data set and plots.

Figure 2.3 shows the transplant curves overlaid with the naive KM that censors subjects at death. There is no difference in the initial portion as no deaths have yet intervened, but the final portion overstates the transplant outcome by more than 10%.

1. The key problem with the naive estimate is that subjects who die can never have a transplant. The result of censoring them is an estimate of the "fraction who would be transplanted, if death before transplant were abolished". This is not a real world quantity.

2. In order to estimate this fictional quantity one needs to assume that death is uninformative with respect to future disease progression. The early deaths in months 0–2, before transplant begins, are however a very different class of patient. Non-informative censoring is untenable.

We are left with an unreliable estimate of an uninteresting quantity. Mislabeling any true state as censoring is always a mistake, one that will not be repeated here. Here is the code for figure 2.3. The use of a logical (true/false) as the status variable in the `Surv` call leads to ordinary survival calculations.

```
> badfit <- survfit(Surv(tstart, tstop, event=="SCT") ~ trt,
                          id=id, mdata, subset=(priortx==0))
> layout(matrix(c(1,1,1,2,3,4), 3,2), widths=2:1)
> oldpar <- par(mar=c(5.1, 4.1, 1.1, .1))
> plot(badfit, fun="event", xmax=48, xaxt='n', col=1:2, lty=2, lwd=2,
       xlab="Months from enrollment", ylab="P(state)")
> axis(1, xtime, xtime)
> lines(sfit3[,2], xmax=48, col=1:2, lwd=2)
> legend(24, .3, c("Arm A", "Arm B"), lty=1, lwd=2,
         col=1:2, bty='n', cex=1.2)
> par(mar=c(4,.1,1,1))
> crisk(c("Entry", "transplant"), alty=2, cex=1.2)
> crisk(c("Entry","transplant", "Death"), cex=1.2)
> par(oldpar)
> layout(1)
```

Complete response is a goal of the initial therapy; figure 2.4 looks more closely at this. As was noted before arm B has an increased number of late responses. The duration of response is also increased: the solid curves show the number of subjects still in response, and we see that they spread farther apart than the dotted "ever in response" curves. The figure shows only the first eight months in order to better visualize the details, but continuing the curves out to 48 months reveals a similar pattern. Here is the code to create the figure.

```
> cr2 <- mdata$event
> cr2[cr2=="SCT"] <- "none" # ignore transplants
> crsurv <- survfit(Surv(tstart, tstop, cr2) ~ trt,
                    data= mdata, id=id, influence=TRUE)
> layout(matrix(c(1,1,2,3), 2,2), widths=2:1)
> oldpar <- par(mar=c(5.1, 4.1, 1.1, .1))
> plot(sfit2[,2], lty=3, lwd=2, col=1:2, xmax=12,
       xlab="Months", ylab="CR")
> lines(crsurv[,2], lty=1, lwd=2, col=1:2)
> par(mar=c(4, .1, 1, 1))
> crisk( c("Entry","CR", "Death"), alty=3)
> state3(c("Entry", "CR", "Death/Relapse"))
> par(oldpar)
> layout(1)
```

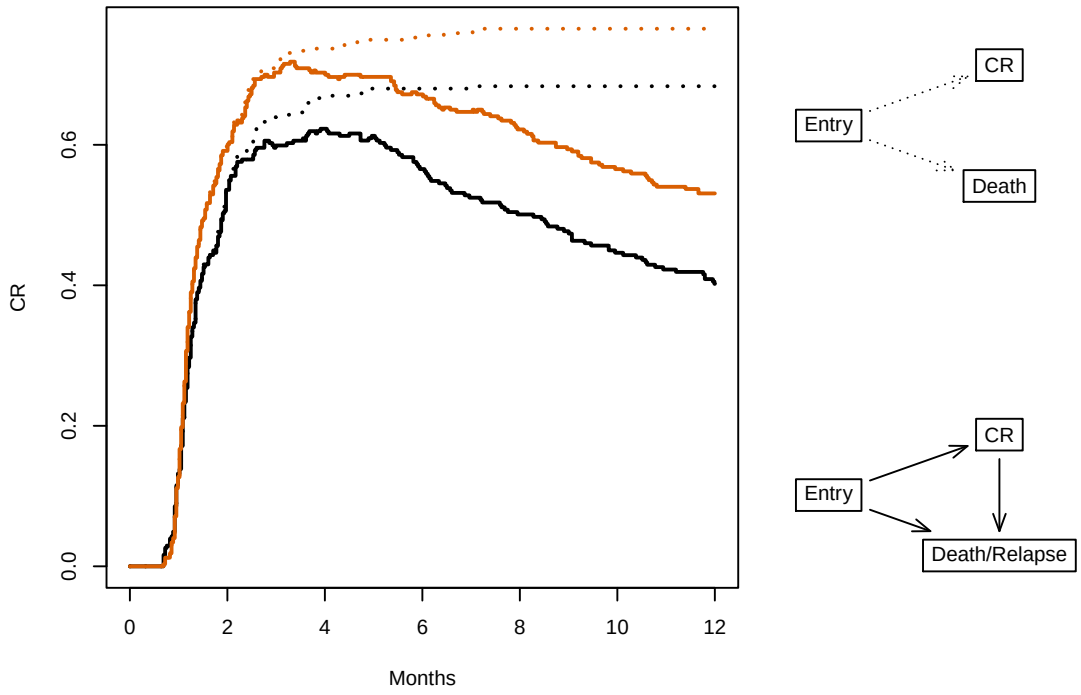


Figure 2.4: Models for 'ever in CR' and 'currently in CR'; the only difference is an additional transition. Both models ignore transplant.

The above code created yet another event variable so as to ignore transitions to the transplant state. They become a non-event, in the same way that extra lines with a status of zero are used to create time-dependent covariates for a Cox model fit.

The `survfit` call above included the `influence=TRUE` argument, which causes the influence array to be calculated and returned. It contains, for each subject, that subject's influence on the time by state matrix of results and allows for calculation of the standard error of the restricted mean. We will return to this in a later section.

```
> print(crsurv, rmean=48, digits=2)
Call: survfit(formula = Surv(tstart, tstop, cr2) ~ trt, data = mdata,
    id = id, influence = TRUE)

                n nevent rmean se(rmean)*
trt=A, (s0)   693      0   7.1       0.78
trt=B, (s0)   739      0   5.6       0.65
trt=A, CR     693    206  16.3       1.13
trt=B, CR     739    248  21.2       1.12
trt=A, SCT    693      0   0.0       0.00
trt=B, SCT    739      0   0.0       0.00
trt=A, relapse 693   109   4.3       0.56
trt=B, relapse 739   117   5.5       0.61
trt=A, death  693    171  20.2       1.10
trt=B, death  739    149  15.6       1.01
   *restricted mean time in state (max time = 48 )
```

The restricted mean time in the CR state is extended by 21.2 - 16.3 = 4.89 months. A question which immediately gets asked is whether this difference is "significant", to which there are two answers. The first and more important is to ask whether 5 months is an important gain from either a clinical or patient perspective. The overall restricted mean survival for the study is approximately 30 of the first 48 months post entry (use `print(sfit1, rmean=48)`); on this backdrop an extra 5 months in CR might or might not be an meaningful advantage from a patient's point of view. The less important answer is to test whether the apparent gain is sufficiently rare from a mathematical point of view, i.e., "statistical" significance. The standard errors of the two values are 1.1 and 1.1, and since they are based on disjoint subjects the values are independent, leading to a standard error for the difference of $\sqrt{1.1^2 + 1.1^2} = 1.6$. The 5 month difference is more than 3 standard errors, so highly significant.

In summary

- Arm B adds late complete responses (about 4%); there are 206/317 in arm A vs. 248/329 in arm B.
- The difference in 4 year survival is about 6%.
- There is approximately 2 months longer average duration of CR (of 48).

CR $\rightarrow$ transplant is the target treatment path for a patient; given the improvements listed above why does figure 2.2 show no change in the number transplanted? Figure 2.5 shows the transplants broken down by whether this happened before or after complete response. Most

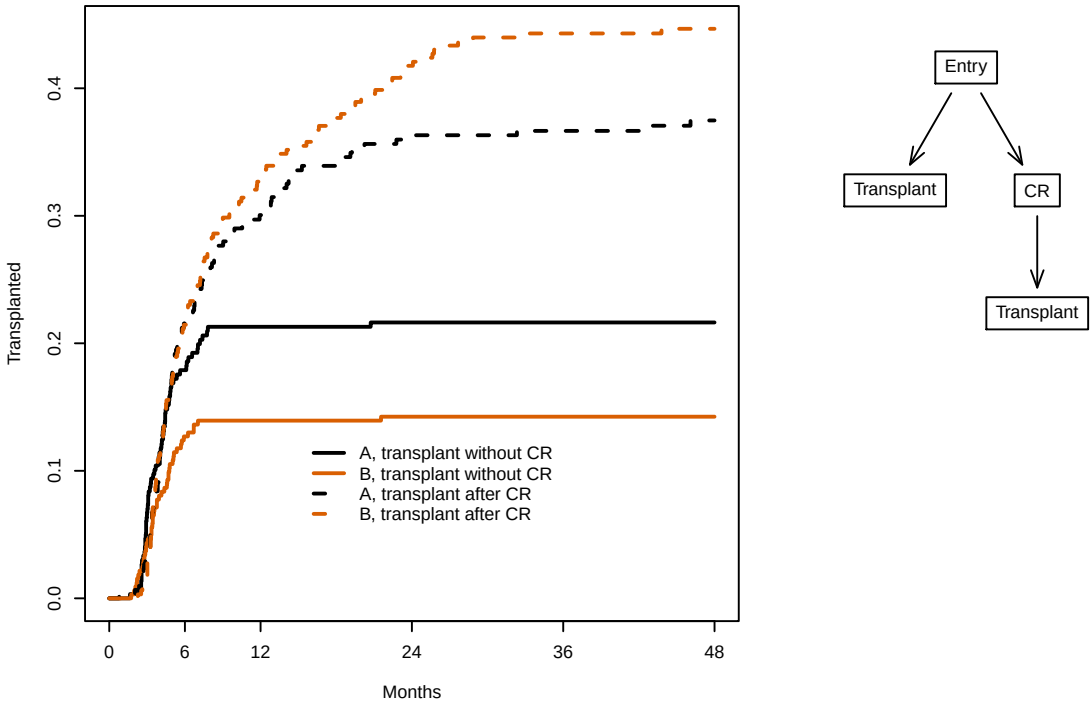


Figure 2.5: Transplant status of the subjects, broken down by whether it occurred before or after CR.

of the non-CR transplants happen by 10 months. One possible explanation is that once it is apparent to the patient/physician pair that CR is not going to occur, they proceed forward with other treatment options. The extra CR events on arm B, which occur between 2 and 8 months, lead to a consequent increase in transplant as well, but at a later time of 12–24 months: for a subject in CR we can perhaps afford to defer the transplant date.

Computation is again based on a manipulation of the event variable: in this case dividing the transplant state into two sub-states based on the presence of a prior CR. The code makes use of the time-dependent covariate `priorcr`. (Because of scheduling constraints within a hospital it is unlikely that a CR that is within a few days prior to transplant could have affected the decision to schedule a transplant, however. An alternate breakdown that might be useful would be "transplant without CR or within 7 days after CR" versus those that are more than a week later. There are many sensible questions that can be asked.)

```
> event2 <- with(mdata, ifelse(event=="SCT" & priorcr==1, 6,
                 as.numeric(event)))
> event2 <- factor(event2, 1:6, c(levels(mdata$event), "SCT after CR"))
> txsurv <- survfit(Surv(tstart, tstop, event2) ~ trt, mdata, id=id,
                    subset=(priortx ==0))
> dim(txsurv) # number of strata by number of states
strata states
     2      6
> txsurv$states # Names of states
[1] "(s0)"         "CR"           "SCT"          "relapse"
[5] "death"        "SCT after CR"
> layout(matrix(c(1,1,1,2,2,0),3,2), widths=2:1)
> oldpar <- par(mar=c(5.1, 4.1, 1,.1))
> plot(txsurv[,c(3,6)], col=1:2, lty=c(1,1,2,2), lwd=2, xmax=48,
       xaxt='n', xlab="Months", ylab="Transplanted")
> axis(1, xtime, xtime)
> legend(15, .13, c("A, transplant without CR", "B, transplant without CR",
                    "A, transplant after CR", "B, transplant after CR"),
         col=1:2, lty=c(1,1,2,2), lwd=2, bty='n')
> state4()  # add the state figure
> par(oldpar)
```

Figure 2.6 shows the full set of state occupancy probabilities for the cohort over the first 4 years. At each point in time the curves estimate the fraction of subjects currently in that state. The total who are in the transplant state peaks at about 9 months and then decreases as subjects relapse or die; the curve rises whenever someone receives a transplant and goes down whenever someone leaves the state. At 36 months treatment arm B (dashed) has a lower fraction who have died, the survivors are about evenly split between those who have received a transplant and those whose last state is a complete response (only a few of the latter are post transplant). The fraction currently in relapse – a transient state – is about 5% for each arm. The figure omits the curve for "still in the entry state". The reason is that at any point in time the sum of the 5 possible states is 1 — everyone has to be somewhere. Thus one of the curves is redundant, and the fraction still in the entry state is the least interesting of them.

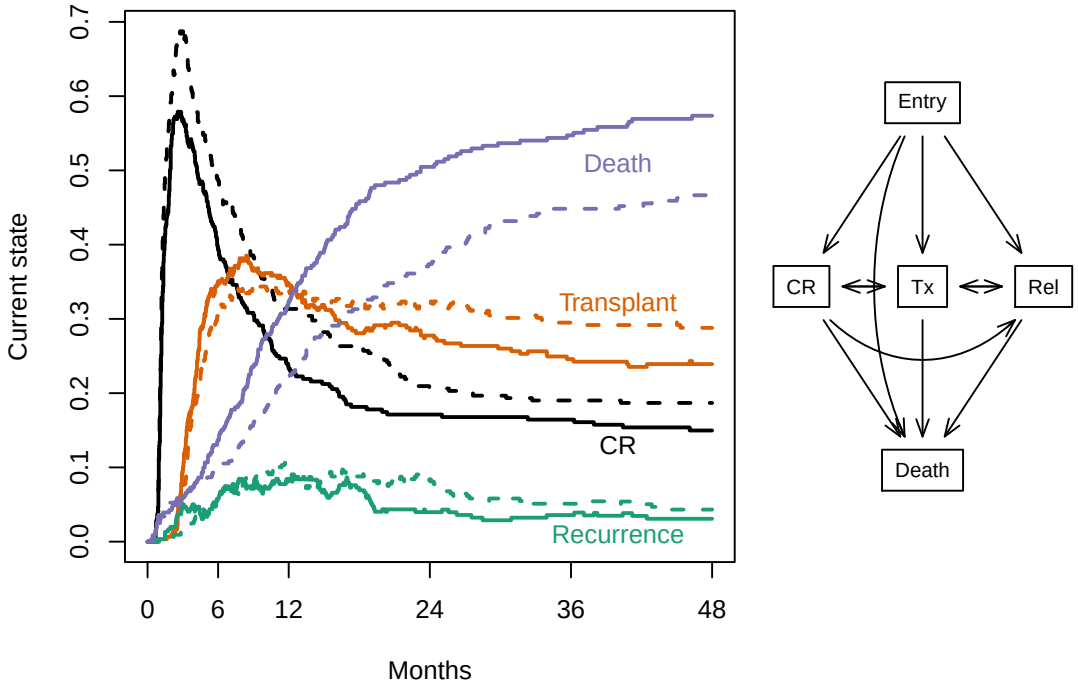


Figure 2.6: The full multi-state curves for the two treatment arms.

```
> sfit4 <- survfit(Surv(tstart, tstop, event) ~ trt, mdata, id=id)
> sfit4$transitions
         to
from       CR SCT relapse death (censored)
  (s0)    443 106      13    55         29
  CR        0 159     168    17        110
  SCT      11   0      45   149        158
  relapse   0  99       0    99         28
  death     0   0       0     0          0
> layout(matrix(1:2,1,2), widths=2:1)
> oldpar <- par(mar=c(5.1, 4.1, 1,.1))
> plot(sfit4, col=rep(1:4,each=2), lwd=2, lty=1:2, xmax=48, xaxt='n',
       xlab="Months", ylab="Current state")
> axis(1, xtime, xtime)
> text(c(40, 40, 40, 40), c(.51, .13, .32, .01),
       c("Death", "CR", "Transplant", "Recurrence"), col=c(4,1,2,3))
> par(mar=c(5.1, .1, 1, .1))
> state5()
> par(oldpar)
```

The transitions table above shows 55 direct transitions from entry to death, i.e., subjects who die without experiencing any of the other intermediate points, 159 who go from CR to transplant (as expected), 11 who go from transplant to CR, etc. No one was observed to go from relapse to CR in the data set, this serves as a data check since it should not be possible per the data entry plan.

2.5 Influence matrix

For one of the curves above we returned the influence array. For each value in the matrix P = probability in state and each subject i in the data set, this contains the effect of that subject on each value in P. Formally,

$$D_{ij}(t) = \left.\frac{\partial p_j(t)}{\partial w_i}\right|_w$$

where $D_{ij}(t)$ is the influence of subject i on $p_j(t)$, and $p_j(t)$ is the estimated probability for state j at time t. This is known as the infinitesimal jackknife (among other labels).

```
> crsurv <- survfit(Surv(tstart, tstop, cr2) ~ trt,
                    data= mdata, id=id, influence=TRUE)
> curveA <- crsurv[1,]  # select treatment A
> dim(curveA)    # P matrix for treatement A
strata states
     1      5
> curveA$states
[1] "(s0)"    "CR"      "SCT"     "relapse" "death"
```

```
> dim(curveA$pstate)  # 426 time points, 5 states
[1] 426   5
> dim(curveA$influence) # influence matrix for treatment A
[1] 317 426   5
> table(myeloid$trt)
  A   B
317 329
```

For treatment arm A there are 317 subjects and 426 time points in the P matrix. The influence array has subject as the first dimension, and for each subject it has an image of the P matrix containing that subject's influence on each value in P, i.e., `influence[1, ,]` is the influence of subject 1 on P. For this data set everyone starts in the entry state, so $p(0) =$ the first row of `pstate` will be (1, 0, 0, 0, 0) and the influence of each subject on this row is 0; this does not hold if not all subjects start in the same state.

As an exercise we will calculate the mean time in state out to 48 weeks. This is the area under the individual curves from time 0 to 48. Since the curves are step functions this is simple sum of rectangles, treating any intervals after 48 months as having 0 width.

```
> t48 <- pmin(48, curveA$time)
> delta <- diff(c(t48, 48))  # width of intervals
> rfun <- function(pmat, delta) colSums(pmat * delta)  #area under the curve
> rmean <- rfun(curveA$pstate, delta)
> # Apply the same calculation to each subject's influence slice
> inf <- apply(curveA$influence, 1, rfun, delta=delta)
> # inf is now a 5 state by 310 subject matrix, containing the IJ estimates
> #  on the AUC or mean time.  The sum of squares is a variance.
> se.rmean <- sqrt(rowSums(inf^2))
> round(rbind(rmean, se.rmean), 2)
         [,1]  [,2] [,3] [,4]  [,5]
rmean    7.10 16.34    0 4.31 20.24
se.rmean 0.78  1.13    0 0.56  1.10
> print(curveA, rmean=48, digits=2)
Call: survfit(formula = Surv(tstart, tstop, cr2) ~ trt, data = mdata,
    id = id, influence = TRUE)

          n nevent rmean se(rmean)*
(s0)    693      0   7.1       0.78
CR      693    206  16.3       1.13
SCT     693      0   0.0       0.00
relapse 693    109   4.3       0.56
death   693    171  20.2       1.10
   *restricted mean time in state (max time = 48 )
```

The last lines verify that this is exactly the calculation done by the `print.survfitms` function; the results can also be found in the `table` component returned by `summary.survfitms`.

In general, let U_i be the influence of subject i. For some function $f(P)$ of the probability in state matrix `pstate`, the influence of subject i will be $\delta_i = f(P + U_i) - f(P)$ and the infinitesimal jackknife estimate of variance will be $\sum_i \delta^2$. For the simple case of adding up rectangles $f(P+U_i) - f(P) = f(U_i)$ leading to particularly simple code, but this will not always be the case.

2.6 Differences in survival

There is a single function `survdiff` to test for differences between 2 or more survival curves. It implements the G^ρ family of Fleming and Harrington [**?**]. A single parameter ρ controls the weights given to different survival times, $\rho = 0$ yields the log-rank test and $\rho = 1$ the Peto-Wilcoxon. Other values give a test that is intermediate to these two. The default value is $\rho = 0$. The log-rank test is equivalent to the score test from a Cox model with the group as a factor variable.

The interpretation of the formula is the same as for `survfit`, i.e., variables on the right hand side of the equation jointly break the patients into groups.

```
> survdiff(Surv(time, status) ~ x, aml)
Call:
survdiff(formula = Surv(time, status) ~ x, data = aml)

                N Observed Expected (O-E)^2/E (O-E)^2/V
x=Maintained    11        7    10.69      1.27       3.4
x=Nonmaintained 12       11     7.31      1.86       3.4

 Chisq= 3.4  on 1 degrees of freedom, p= 0.07
```

2.7 Robust variance

The `survfit`, `coxph` and `surveg` routines all allow for the computation of an infintisimal jackknife variance estimate. This estimator is widely used in statistics under several names: in generalized estimating equation (GEE) models is is known as the working-independence variance; in linear models as White's estimate, and in survey sampling as the Horvitz-Thompsen estimate. One feature of the estimate is that it is robust to model misspecification; the argument `robust=TRUE` to any of the three routines will invoke the estimator. If `robust=TRUE` and there is no `cluster` or `id` argument, the program will assume that each row of data is from a unique subject, a possibly questionable assumption. It is better to provide the grouping explicitly.

If the robust argument is missing (the usual case), then if there is an `cluster` argument, non-integer case weights, or there is an `id` argument and at least one id has multiple events, then the code assumes that robust=TRUE, and otherwise assumes robust=FALSE. These are cases where the robust variance is most likely to be desirable. If there is an `id` argument but no `cluster` the default is to cluster by id. If there are non-integer weights but no clustering information is provided (id or cluster statement), the code will assume that each row of data is a separate subject. If the response is of (time1, time2) form this assumption is almost certainly

incorrect, but the model based variance would have the same assumption so it is a choice between two evils. Responsibility falls on the user to clarify the proper clustering. (A error or warning from the code would be defensible, but the package author so dislikes packages that chatter warnings all the time that he is loath to do so.)

The infinitesimal jackknife (IJ) matrix contains the influence of each subject on the estimator; formally the derivative with respect to each subject's case weight. For a single simple survival curve that has k unique values, for instance, the IJ matrix will have n rows and k columns, one row per subject. Columns of the matrix sum to zero, by definition, and the variance at a time point t will be the column sums of $(IJ)^2$. For a competing risk problem the `crfit` object above will contain a matrix `pstate` with k rows and one column for each state, where k is the number of unique time points; and the IJ is an array of dimension (n, k, p). In the case of simple survival and all case weights =1, the IJ variance collapses to the well known Greenwood variance estimate.

2.8 State space figures

The state space figures in the above example were drawn with a simple utility function `statefig`. It has two primary arguments along with standard graphical options of color, line type, etc.

1. A layout vector or matrix. A vector with values of (1, 3, 1) for instance will allocate one state, then a column with 3 states, then one more state, proceeding from left to right. A matrix with a single row will do the same, whereas a matrix with one column will proceed from top to bottom.

2. A k by k connection matrix C where k is the number of states. If $C_{ij} \neq 0$ then an arrow is drawn from state i to state j. The row or column names of the matrix are used to label the states. The lines connecting the states can be straight or curved, see the help file for an example.

The first few state space diagrams were competing risk models, which use the following helper function. It accepts a vector of state names, where the first name is the starting state and the remainder are the possible outcomes.

```
> crisk <- function(what, horizontal = TRUE, ...) {
      nstate <- length(what)
      connect <- matrix(0, nstate, nstate,
                        dimnames=list(what, what))
      connect[1,-1] <- 1  # an arrow from state 1 to each of the others
      if (horizontal) statefig(c(1, nstate-1),  connect, ...)
      else statefig(matrix(c(1, nstate-1), ncol=1), connect, ...)
  }
```

This next function draws a variation of the illness-death model. It has an initial state, an absorbing state (normally death), and an optional intermediate state.

```
> state3 <- function(what, horizontal=TRUE, ...) {
      if (length(what) != 3) stop("Should be 3 states")
```

```
    connect <- matrix(c(0,0,0, 1,0,0, 1,1,0), 3,3,
                      dimnames=list(what, what))
    if (horizontal) statefig(1:2, connect, ...)
    else statefig(matrix(1:2, ncol=1), connect, ...)
}
```

The most complex of the state space figures has all 5 states.

```
> state5 <- function(what, ...) {
    sname <- c("Entry", "CR", "Tx", "Rel", "Death")
    connect <- matrix(0, 5, 5, dimnames=list(sname, sname))
    connect[1, -1] <- c(1,1,1, 1.4)
    connect[2, 3:5] <- c(1, 1.4, 1)
    connect[3, c(2,4,5)] <- 1
    connect[4, c(3,5)]  <- 1
    statefig(matrix(c(1,3,1)), connect, cex=.8, ...)
}
```

For figure 2.5 I want a third row with a single state, but don't want that state centered. For this I need to create my own (x,y) coordinate list as the layout parameter. Coordinates must be between 0 and 1.

```
> state4 <- function() {
    sname <- c("Entry", "CR", "Transplant", "Transplant")
    layout <- cbind(x =c(1/2, 3/4, 1/4, 3/4),
                    y =c(5/6, 1/2, 1/2, 1/6))
    connect <- matrix(0,4,4, dimnames=list(sname, sname))
    connect[1, 2:3] <- 1
    connect[2,4] <- 1
    statefig(layout, connect)
}
```

The statefig function was written to do "good enough" state space figures quickly and easily, in the hope that users will find it simple enough that diagrams are drawn early and often. Packages designed for directed acyclic graphs (DAG) such as diagram, DiagrammeR, or dagR are far more flexible and can create more nuanced and well decorated results.

2.8.1 Further notes

The Aalen-Johansen method used by `survfit` does not account for interval censoring, also known as panel data, where a subject's current state is recorded at some fixed time such as a medical center visit but the actual times of transitions are unknown. Such data requires further assumptions about the transition process in order to model the outcomes and has a more complex likelihood. The `msm` package, for instance, deals with data of this type. If subjects reliably come in at regular intervals then the difference between the two results can be small, e.g., the `msm` routine estimates time until progression *occurred* whereas `survfit` estimates time until progression was *observed*.

- When using multi-state data to create Aalen-Johansen estimates, individuals are not allowed to have gaps in the middle of their time line. An example of this would be a data set with (0, 30, pcm] and (50,70, death] as the two observations for a subject where the time from 30-70 is not accounted for.
- Subjects must stay in the same group over their entire observation time, i.e., variables on the right hand side of the equation cannot be time-dependent.
- A transition to the same state is allowed, e.g., observations of (0,50, 1], (50, 75, 3], (75, 89, 4], (89, 93, 4] and (93, 100, 4] for a subject who goes from entry to state 1, then to state 3, and finally to state 4. However, a warning message is issued for the data set in this case, since stuttering may instead be the result of a coding mistake. The same result is obtained if the last three observations were collapsed to a single row of (75, 100, 4].

Chapter 3

Cox model

The most commonly used models for survival data are those that model the transition rate from state to state, i.e., the arrows of figure 1.1. They are Poisson regression (3.1), the Cox or proportional hazards model (3.2) and the Aalen additive regression model (3.3), of which the Cox model is far and away the most popular. As seen in the equations they are closely related.

$$\lambda(t) = e^{beta_0+\beta_1 x_1+\beta_2 x_2+\ldots} \tag{3.1}$$

$$\lambda(t) = e^{\beta_0(t)+\beta_1 x_1+\beta_2 x_2+\ldots}$$

$$= \lambda_0(t) e^{\beta_1 x_1+\beta_2 x_2+\ldots} \tag{3.2}$$

$$\lambda(t) = \beta_0(t) + \beta_1(t)x_1 + \beta_2(t)x_2 + \ldots \tag{3.3}$$

(Textbooks on survival use $\lambda(t)$, $\alpha(t)$ and $h(t)$ in about equal proportions. There is no good argument for any one versus another, but this author started his career with books that used λ so that is what you will get.)

3.1 One event type, one event per subject

Single event data is the most common use for Cox models. We will use a data set that contains the survival of 228 patients with advanced lung cancer.

```
> options(show.signif.stars=FALSE)  # display statistical intelligence
> cfit1 <- coxph(Surv(time, status) ~ age + sex + wt.loss, data=lung)
> print(cfit1, digits=3)
Call:
coxph(formula = Surv(time, status) ~ age + sex + wt.loss, data = lung)

             coef exp(coef) se(coef)     z      p
age       0.02009   1.02029  0.00966  2.08 0.0377
sex      -0.52103   0.59391  0.17435 -2.99 0.0028
wt.loss   0.00076   1.00076  0.00619  0.12 0.9024
```

```
Likelihood ratio test=14.7  on 3 df, p=0.00212
n= 214, number of events= 152
   (14 observations deleted due to missingness)
> summary(cfit1, digits=3)
Call:
coxph(formula = Surv(time, status) ~ age + sex + wt.loss, data = lung)

  n= 214, number of events= 152
   (14 observations deleted due to missingness)

              coef  exp(coef)   se(coef)      z Pr(>|z|)
age      0.0200882  1.0202913  0.0096644  2.079   0.0377
sex     -0.5210319  0.5939074  0.1743541 -2.988   0.0028
wt.loss  0.0007596  1.0007599  0.0061934  0.123   0.9024

        exp(coef) exp(-coef) lower .95 upper .95
age        1.0203     0.9801    1.0011    1.0398
sex        0.5939     1.6838    0.4220    0.8359
wt.loss    1.0008     0.9992    0.9887    1.0130

Concordance= 0.612  (se = 0.027 )
Likelihood ratio test= 14.67  on 3 df,   p=0.002
Wald test            = 13.98  on 3 df,   p=0.003
Score (logrank) test = 14.24  on 3 df,   p=0.003
> anova(cfit1)
Analysis of Deviance Table
 Cox model: response is Surv(time, status)
Terms added sequentially (first to last)

         loglik  Chisq Df Pr(>|Chi|)
NULL    -680.39
age     -677.78 5.2273  1   0.022235
sex     -673.06 9.4268  1   0.002138
wt.loss -673.06 0.0150  1   0.902592
```

As is usual with R modeling functions, the default `print` routine gives a short summary and the `summary` routine a longer one. The `anova` command shows tests for each term in a model, added sequentially. We purposely avoid the innane addition of "significant stars" to any printout. Age and gender are strong predictors of survival, but the amount of recent weight loss was not influential.

The following functions can be used to extract portions of a `coxph` object.

- `coef` or `coefficients`: the vector of coefficients
- `concordance`: the concordance statistic for the model fit

- `fitted`: the fitted values, also known as linear predictors
- `logLik`: the partial likelihood
- `model.frame`: the model.frame of the data used in the fit
- `model.matrix`: the X matrix used in the fit
- `nobs`: the number of observations
- `predict`: a vector or matrix of predicted values
- `residuals`: a vector of residuals
- `vcov`: the variance-covariance matrix
- `weights`: the vector of case weights used in the fit

Further details about the contents of a `coxph` object can be found by `help('coxph.object')`.

The global `na.action` function has an important effect on the returned vector of residuals, as shown below. This can be set per fit, but is more often set globally via the `options()` function.

```
> cfit1a <- coxph(Surv(time, status) ~ age + sex + wt.loss, data=lung,
                  na.action = na.omit)
> cfit1b <- coxph(Surv(time, status) ~ age + sex + wt.loss, data=lung,
                  na.action = na.exclude)
> r1 <- residuals(cfit1a)
> r2 <- residuals(cfit1b)
> length(r1)
[1] 214
> length(r2)
[1] 228
```

The fits have excluded 14 subjects with missing values for one or more covariates. The residual vector `r1` omits those subjects from the residuals, while `r2` returns a vector of the same length as the original data, containing NA for the omitted subjects. Which is preferred depends on what you want to do with the residuals. For instance `mean(r1)` is simpler using the first while `plot(lung$ph.ecog, r2)` is simpler with the second.

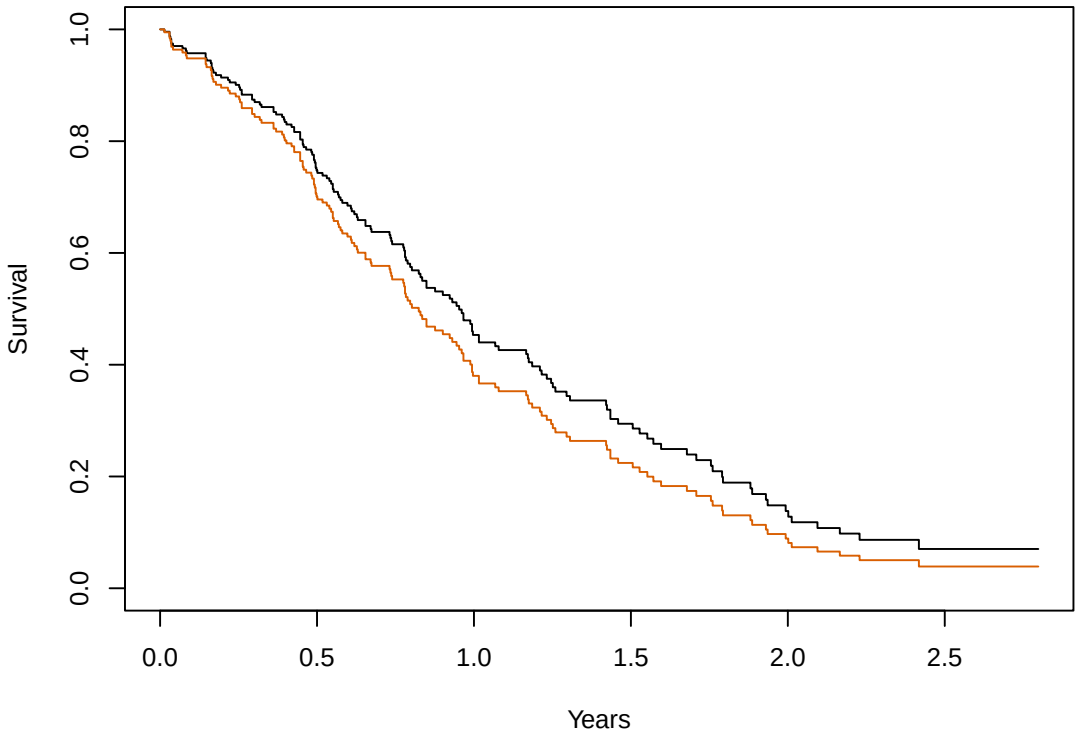
Stratified Cox models are obtained by adding one or more `strata` terms to the model formula. In a stratified model each subject is compared only to subjects within their own stratum for computing the partial likelihood, and then the final results are summed over the strata. A useful rule of thumb is that a variable included as a stratum is adjusted for in the most general way, at the price of not having an estimate of its effect. One common use of strata is to adjust for the enrolling institution in a multi-center study, as below. We see that in this case the effect of stratification is slight.

```
> cfit2 <- coxph(Surv(time, status) ~ age + sex + wt.loss + strata(inst),
                 data=lung)
> round(cbind(simple= coef(cfit1), stratified=coef(cfit2)), 4)
```

```
          simple stratified
age       0.0201     0.0235
sex      -0.5210    -0.5160
wt.loss   0.0008    -0.0017
```

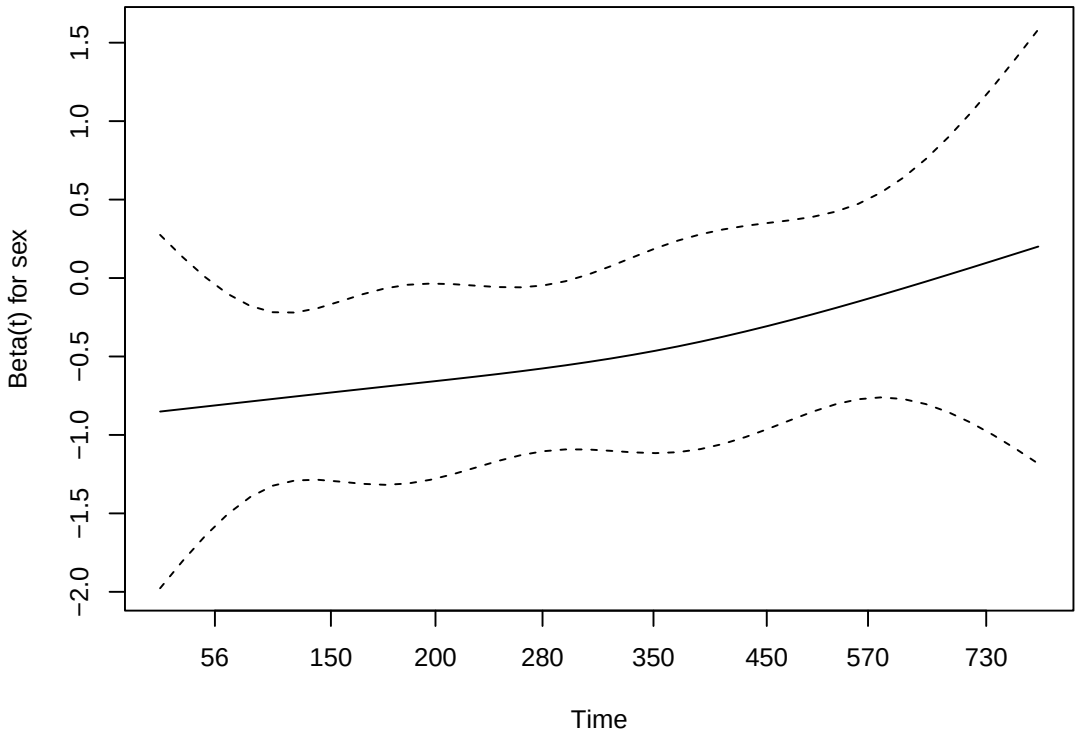
Predicted survival curves from a Cox model are obtained using the `survfit` function. Since these are predictions from a model, it is necessary to specify *whom* the predictions should be for, i.e., one or more sets of covariate values. Here is an example.

```
> dummy <- expand.grid(age=c(50, 60), sex=1, wt.loss=5)
> dummy
  age sex wt.loss
1  50   1       5
2  60   1       5
> csurv1 <- survfit(cfit1, newdata=dummy)
> csurv2 <- survfit(cfit2, newdata=dummy)
> dim(csurv1)
data
   2
> dim(csurv2)
strata   data
    18      2
> plot(csurv1, col=1:2, xscale=365.25, xlab="Years", ylab="Survival")
> dummy2 <- data.frame(age=c(50, 60), sex=1:2, wt.loss=5, inst=c(6,11))
> csurv3 <- survfit(cfit2, newdata=dummy2)
> dim(csurv3)
strata
     2
```



The simplifying aspects of the Cox model that make is so useful are exactly those that should be verified, namely proportional hazards, additivity, linearity, and lack of any high leverage points. The first can be checked with the `cox.zph` function.

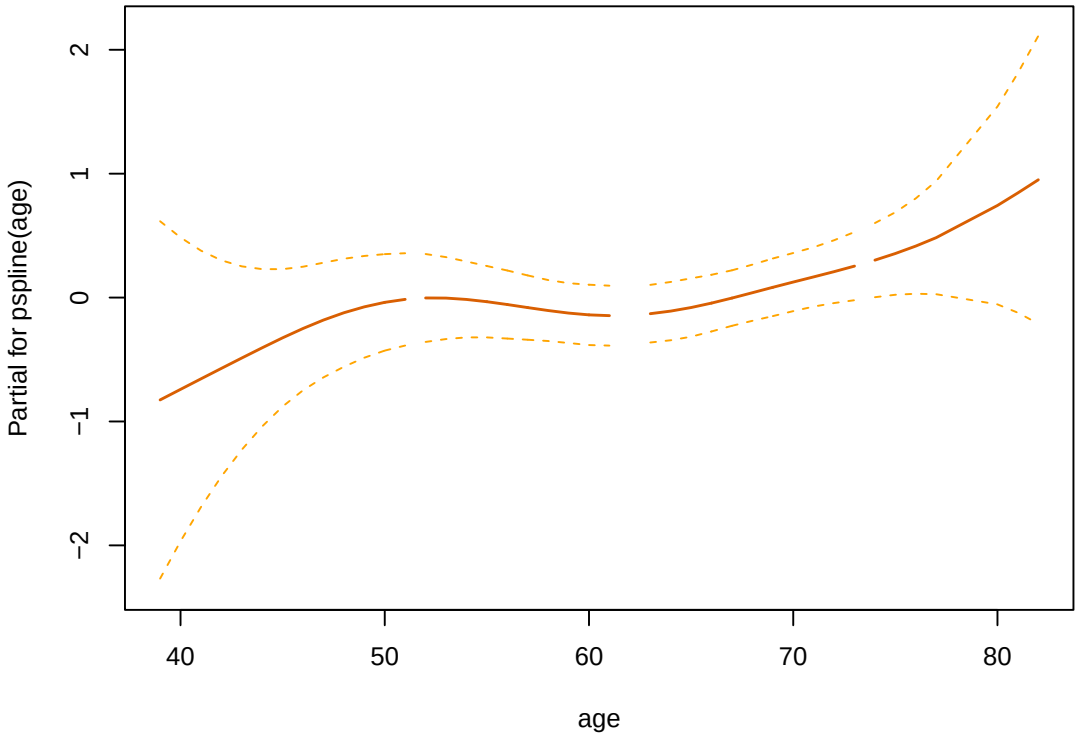
```
> zp1 <- cox.zph(cfit1)
> zp1
         chisq df    p
age     0.5077  1 0.48
sex     2.5489  1 0.11
wt.loss 0.0144  1 0.90
GLOBAL  3.0051  3 0.39
> plot(zp1[2], resid=FALSE)
> abline(coef(fit1)[2] ,0, lty=3)
```



None of the test statistics for PH are remarkable. A simple check for linearity of age is to replace the term with a smoothing spline.

```
> cfit3 <- coxph(Surv(time, status) ~ pspline(age) + sex + wt.loss, lung)
> print(cfit3, digits=2)
Call:
coxph(formula = Surv(time, status) ~ pspline(age) + sex + wt.loss,
    data = lung)

                         coef se(coef)      se2    Chisq  DF     p
pspline(age), linear  0.02011  0.00931  0.00931  4.66393 1.0 0.031
pspline(age), nonlin                             3.02601 3.1 0.402
sex                  -0.53145  0.17549  0.17513  9.17105 1.0 0.002
wt.loss               0.00056  0.00619  0.00618  0.00818 1.0 0.928

Iterations: 4 outer, 12 Newton-Raphson
     Theta= 0.8
Degrees of freedom for terms= 4.1 1.0 1.0
Likelihood ratio test=18  on 6.1 df, p=0.006
n= 214, number of events= 152
   (14 observations deleted due to missingness)
> termplot(cfit3, term=1, se=TRUE)
> cfit4 <- update(cfit1, . ~ . + age*sex)
```

```
> anova(cfit1, cfit4)
Analysis of Deviance Table
 Cox model: response is  Surv(time, status)
 Model 1: ~ age + sex + wt.loss
 Model 2: ~ age + sex + wt.loss + age:sex
   loglik  Chisq Df Pr(>|Chi|)
1 -673.06
2 -672.88 0.3473  1     0.5557
```



The age effect appears reasonbly linear. Additivity can be examined by adding an age by sex interaction, and again is not remarkable.

3.2 Repeating Events

Children with chronic granulotomous disease (CGD) are subject to repeated infections due to a compromised immune system. The `cgd0` data set contains results of a clinical trial of gamma interferon as a treatment, the data set `cdg` contains the data reformatted into a (tstart, tstop, status) form: each child can have multiple rows which describe an interval of time, and status=1 if that interval ends with an infection and 0 otherwise. A model with a single baseline hazard, known as the Andersen-Gill model, can be fit very simply. The study recruited subjects from four types of institutions, and there is an a priori belief that the four classes might recruit a

different type of subject. Adding the hospital category as a strata allows each group to have a different shape of baseline hazard.

```
> cfit1 <- coxph(Surv(tstart, tstop, status) ~ treat + inherit + steroids +
                     age + strata(hos.cat), data=cgd)
> print(cfit1, digits=2)
Call:
coxph(formula = Surv(tstart, tstop, status) ~ treat + inherit +
    steroids + age + strata(hos.cat), data = cgd)

                   coef exp(coef) se(coef)    z     p
treatrIFN-g      -1.113     0.328    0.267 -4.2 3e-05
inheritautosomal  0.430     1.537    0.250  1.7  0.09
steroids          1.258     3.517    0.573  2.2  0.03
age              -0.036     0.964    0.015 -2.4  0.02

Likelihood ratio test=31  on 4 df, p=3.8e-06
n= 203, number of events= 76
```

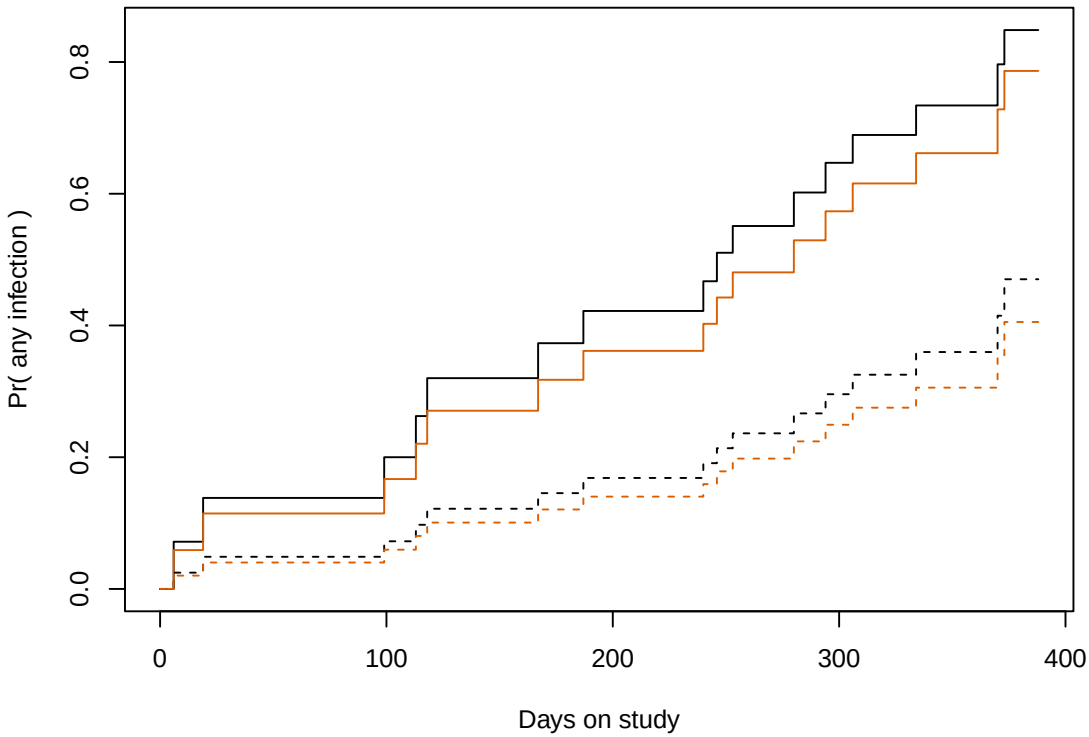
Further examination shows that the fit is problematic in that only 3 of 128 children have `steroids ==1`, so we refit without that variable.

```
> cfit2 <- coxph(Surv(tstart, tstop, status) ~ treat + inherit+
                     age + strata(hos.cat), data=cgd)
> print(cfit2, digits=2)
Call:
coxph(formula = Surv(tstart, tstop, status) ~ treat + inherit +
    age + strata(hos.cat), data = cgd)

                   coef exp(coef) se(coef)    z     p
treatrIFN-g      -1.089     0.337    0.265 -4.1 4e-05
inheritautosomal  0.406     1.500    0.249  1.6  0.10
age              -0.033     0.967    0.015 -2.3  0.02

Likelihood ratio test=27  on 3 df, p=6.6e-06
n= 203, number of events= 76
```

Predicted survival and/or cumulative hazard curves can then be obtained from the fitted model. Prediction requires the user to specifiy *who* to predict; in this case we will use 4 hypothetical subjects on control/interferon treatment, at ages 7 and 20 (near the quantiles). This creates a data frame with 4 rows.

```
> dummy <- expand.grid(age=c(6,12), inherit='X-linked',
                       treat=levels(cgd$treat))
> dummy
  age  inherit   treat
1   6 X-linked placebo
```

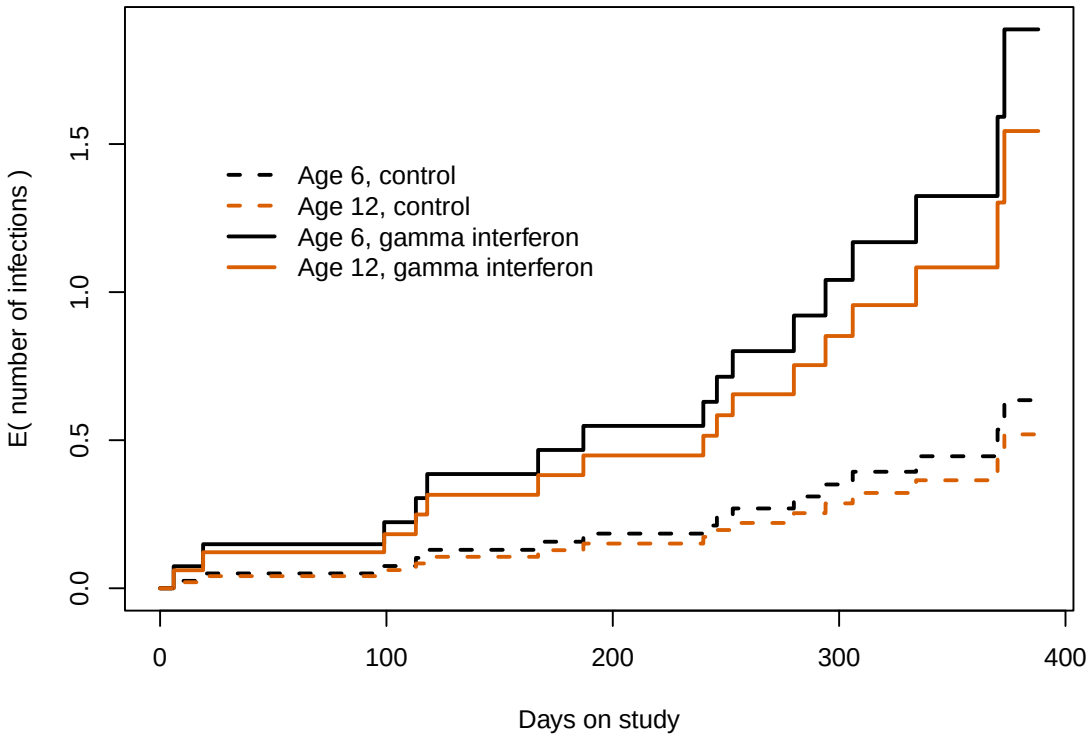
```
2  12 X-linked placebo
3   6 X-linked  rIFN-g
4  12 X-linked  rIFN-g
> csurv <- survfit(cfit2, newdata=dummy)
> dim(csurv)
strata   data
     4      4
> plot(csurv[1,], fun="event", col=1:2, lty=c(1,1,2,2),
       xlab="Days on study", ylab="Pr( any infection )")
```



The resulting object was subscripted in order to make a plot with fewer curves, i.e., predictions for the first level of `hosp.cat`. We see that treatment is effective but the effect of age is small.

Perhaps more interesting in this situation is the expected number of infections, rather than the probability of having at least 1. The former is estimated by the cumulative hazard, which is also returned by the `survfit` routine.

```
> plot(csurv[1,], cumhaz=TRUE, col=1:2, lty=c(1,1,2,2), lwd=2,
       xlab="Days on study", ylab="E( number of infections )")
> legend(20, 1.5, c("Age 6, control", "Age 12, control",
                    "Age 6, gamma interferon", "Age 12, gamma interferon"),
         lty=c(2,2,1,1), col=c(1,2,1,2), lwd=2, bty='n')
```



3.3 Competing risks

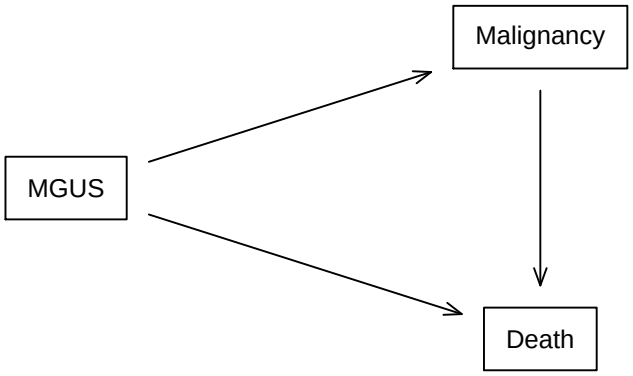
Our third category is models where there is more than one event type, but each subject can have only one transition. This is the setup of competing risks.

3.3.1 MGUS

As an simple multi-state example consider the monoclonal gammopathy data set `mgus2`, which contains the time to a plasma cell malignancy (PCM), usually multiple myleoma, and the time to death for 1384 subjects found to have a condition known as monoclonal gammopathy of undetermined significance (MGUS), based on a particular test. This data set has already appeared in 2.3.2. The time values in the data set are from detection of the condition. Here are a subset of the observations along with a simple state figure for the data.

```
> mgus2[56:59,]
   id age sex dxyr  hgb creat mspike ptime pstat futime death etime
56 56  78   M 1978 10.3   3.0    1.9    29     1     44     1    29
57 57  79   F 1981 13.6   1.3    1.3    84     0     84     1    84
58 58  72   F 1972 13.6   1.2    0.4   321     0    321     1   321
59 59  80   F 1984 10.6   0.9    1.2   147     0    147     1   147
   event
```

```
56   pcm
57 death
58 death
59 death
> sname <- c("MGUS", "Malignancy", "Death")
> smat <- matrix(c(0,0,0, 1,0,0, 1,1,0), 3, 3,
                 dimnames = list(sname, sname))
> statefig(c(1,2), smat)
```



In this data set subject 56 was diagnosed with a PCM 29 months after detection of MGUS and died at 44 months. This subject passes through all three states. The other three listed individuals died without a plasma cell malignancy and traverse one of the arrows; 103 subjects (not shown) are censored before experiencing either event and spend their entire tenure in the leftmost state. The competing risks model will ignore the transition from malignacy to death: the two ending states are "malignancy before death" and "death without malignancy".

The `statefig` function is designed to create simple state diagrams, with an emphasis on ease rather than elegance. See more information in section 2.8.

For competing risks each subject has at most one transition, so the data set only needs one row per subject.

```
> crdata <- mgus2
> crdata$etime <- pmin(crdata$ptime, crdata$futime)
> crdata$event <- ifelse(crdata$pstat==1, 1, 2*crdata$death)
```

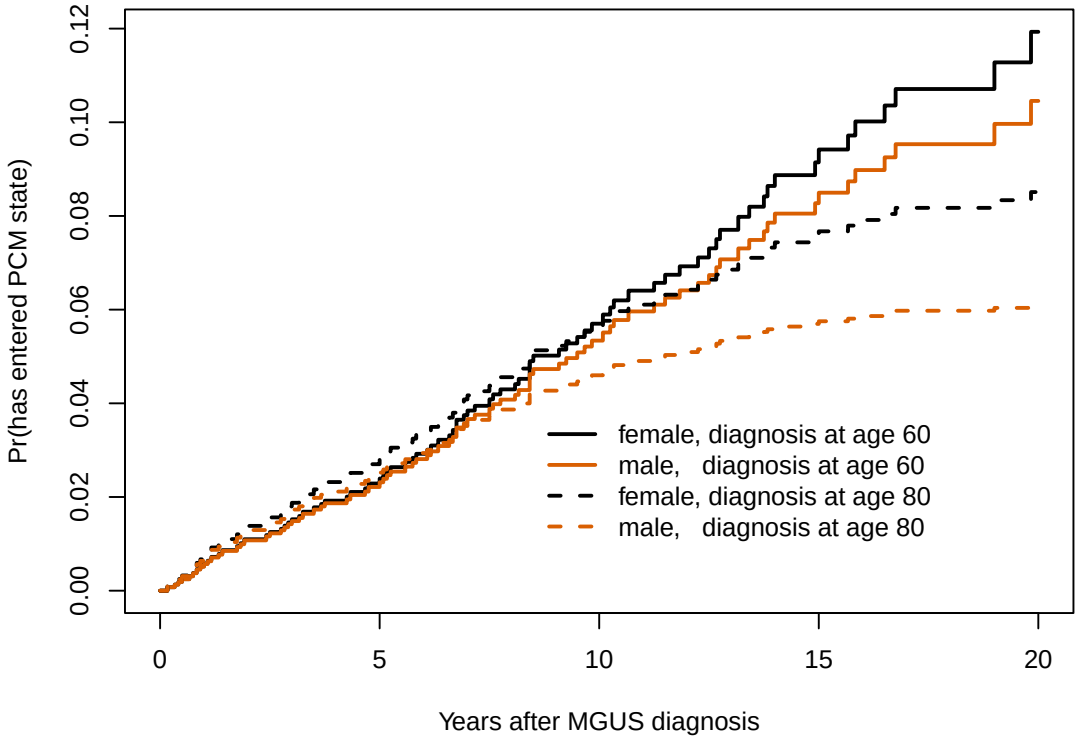
```
> crdata$event <- factor(crdata$event, 0:2, c("censor", "PCM", "death"))
> quantile(crdata$age, na.rm=TRUE)
  0%  25%  50%  75% 100%
  24   63   72   79   96
> table(crdata$sex)
  F   M
631 753
> quantile(crdata$mspike, na.rm=TRUE)
  0%  25%  50%  75% 100%
 0.0  0.6  1.2  1.5  3.0
> cfit <- coxph(Surv(etime, event) ~ I(age/10) + sex + mspike,
                id = id, crdata)
> print(cfit, digits=1)  # narrow the printout a bit
Call:
coxph(formula = Surv(etime, event) ~ I(age/10) + sex + mspike,
    data = crdata, id = id)


1:2           coef exp(coef) se(coef) robust se z     p
  I(age/10)  0.164     1.178    0.084     0.069 2  0.02
  sexM      -0.005     0.995    0.188     0.188 0  0.98
  mspike     0.884     2.421    0.165     0.168 5 2e-07


1:3           coef exp(coef) se(coef) robust se  z      p
  I(age/10)  0.65      1.92     0.04      0.04 17 <2e-16
  sexM       0.39      1.48     0.07      0.07  6  5e-09
  mspike    -0.06      0.94     0.06      0.06 -1    0.3

 States:  1= (s0), 2= PCM, 3= death

Likelihood ratio test=419  on 6 df, p=<2e-16
n= 1373, number of events= 969
   (11 observations deleted due to missingness)
```

The effect of age and sex on non-PCM mortality is profound, which is not a surprise given the median starting age of 72. Death rates rise 678.6 fold per decade of age and the death rate for males is 1.5 times as great as that for females. The size of the serum monoclonal spike has almost no impact on non-PCM mortality. A 1 unit increase changes mortality by only 2%.

The mspike size has a major impact on progression, however; each 1 gram change increases risk by 2.4 fold. The interquartile range of `mspike` is 0.9 grams so this risk increase is clinically important. The effect of age on the progression rate is much less pronounced, with a coefficient only 1/4 that for mortality, while the effect of sex on progression is completely negligible.

Estimates of the probability in state can be simply computed using `survfit`. As with any model, estimates are always for a particular set of covariates. We will use 4 hypothetical subjects, male and female with ages of 60 and 80.

```
> dummy <- expand.grid(sex=c("F", "M"), age=c(60, 80), mspike=1.2)
> csurv  <- survfit(cfit, newdata=dummy)
> plot(csurv[,2], xmax=20*12, xscale=12,
       xlab="Years after MGUS diagnosis", ylab="Pr(has entered PCM state)",
       col=1:2, lty=c(1,1,2,2), lwd=2)
> legend(100, .04, outer(c("female,", "male,  "),
                         c("diagnosis at age 60", "diagnosis at age 80"),
                          paste),
         col=1:2, lty=c(1,1,2,2), bty='n', lwd=2)
```

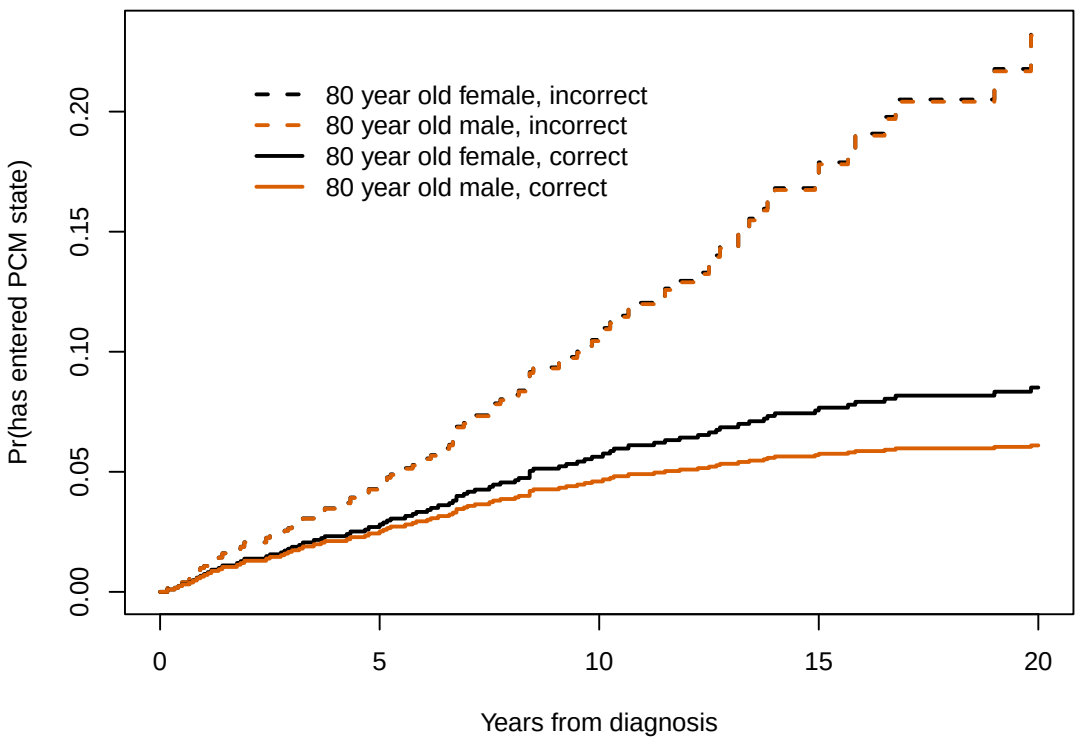


Although sex has no effect on the *rate* of plasma cell malignancy, its effect on the *lifetime probability* of PCM is not zero, however. As shown by the simple Poisson model below, the rate of PCM is about 1% per year. Other work reveals that said rate is almost constant over follow-up time (not shown). Because women in the study have an average lifetime that is 2 years longer than men, their lifetime risk of PCM is higher as well. Very few subjects acquire PCM more than 15 years after a MGUS diagnosis at age 80 for the obvious reason that very few of them will still be alive.

```
> mpfit <- glm(pstat ~ sex -1 + offset(log(ptime)), data=mgus2, poisson)
> exp(coef(mpfit)) * 12   # rate per year
      sexF       sexM
0.01117354 0.01016626
```

A single outcome fit using only time to progression is instructive: we obtain exactly the same coefficients but different absolute risks. This is a basic property of multi-state models: hazards can be explored separately for each transition, but absolute risk must be computed globally. (The estimated cumulative hazards from the two models are also identical). The incorrect curve is a vain attempt to estimate the progression rate which would occur if death could be abolished. It not surprisingly ends up as about 1% per year.

```
> sfit <- coxph(Surv(etime, event=="PCM") ~ I(age/10) + sex + mspike, crdata)
> rbind(single = coef(sfit),
        multi  = coef(cfit)[1:3])
       I(age/10)         sexM    mspike
single 0.1635219 -0.005030024 0.8840781
multi  0.1635219 -0.005030024 0.8840781
> #par(mfrow=c(1,2))
> ssurv <- survfit(sfit, newdata=dummy)
> plot(ssurv[3:4], col=1:2, lty=2, xscale=12, xmax=12*20, lwd=2, fun="event",
       xlab="Years from diagnosis", ylab= "Pr(has entered PCM state)")
> lines(csurv[3:4, 2], col=1:2, lty=1, lwd=2)
> legend(20, .22, outer(c("80 year old female,", "80 year old male,"),
                        c("incorrect", "correct"), paste),
                    col=1:2, lty=c(2,2,1,1), lwd=2, bty='n')
```

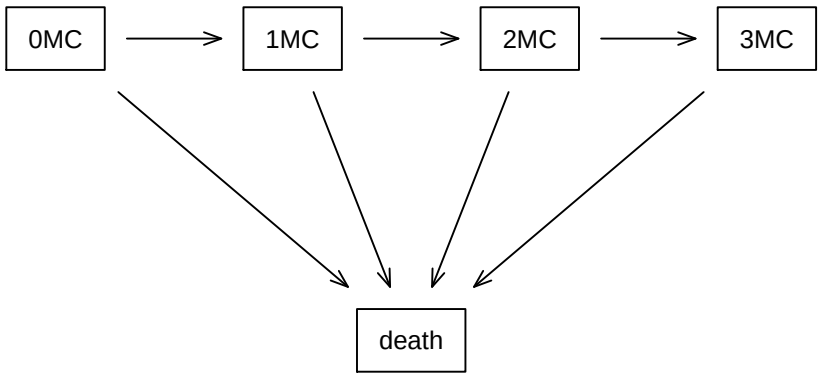


3.4 Multiple event types and multiple events per subject

Non-alcoholic fatty liver disease (NAFLD) is defined by three criteria: presence of greater than 5% fat in the liver (steatosis), absence of other indications for the steatosis such as excessive alcohol consumption or certain medications, and absence of other liver disease [?]. NAFLD is currently responsible for almost 1/3 of liver transplants and it's impact is growing, it is expected to be a major driver of hepatology practice in the coming decade [?], driven at least in part by the growing obesity epidemic. The `nafld` data set includes all patients with a NAFLD diagnosis in Olmsted County, Minnesota between 1997 to 2014 along with up to four age and sex matched controls for each case [?].

We will model the onset of three important components of the metabolic syndrome: diabetes, hypertension, and dyslipidemia, using the model shown below. Subjects have either 0, 1, 2, or all 3 of these metabolic comorbidities.

```
> state5 <- c("0MC", "1MC", "2MC", "3MC", "death")
> tmat <- matrix(0L, 5, 5, dimnames=list(state5, state5))
> tmat[1,2] <- tmat[2,3] <- tmat[3,4] <- 1
> tmat[-5,5] <- 1
> statefig(rbind(4,1), tmat)
```



3.4.1 Data

The NAFLD data is represented as 3 data sets, `nafld1` has one observation per subject containing basline information (age, sex, etc.), nafld2 has information on repeated laboratory tests, e.g. blood pressure, and nafld3 has information on yes/no endpoints. After the case-control set was assembled, we removed any subjects with less than 7 days of follow-up. These subjects add little information, and it prevents a particular confusion that can occur with a multi-day medical visit where two results from the same encounter have different dates. To protect patient confidentiality all time intervals are in days since the index date; none of the dates from the original data were retained. Subject age is their integer age at the index date, and the subject identifier is an arbitrary integer. As a final protection, a 10% random sample of subjects was excluded. As a consequence analyses results will not exactly match the original paper.

Start by building an analysis data set using `nafld1` and `nafld3`.

```
> ndata <- tmerge(nafld1[,1:8], nafld1, id=id, death= event(futime, status))
> ndata <- tmerge(ndata, subset(nafld3, event=="nafld"), id,
                  nafld= tdc(days))
> ndata <- tmerge(ndata, subset(nafld3, event=="diabetes"), id = id,
                  diabetes = tdc(days), e1= cumevent(days))
> ndata <- tmerge(ndata, subset(nafld3, event=="htn"),  id = id,
                  htn = tdc(days), e2 = cumevent(days))
> ndata <- tmerge(ndata, subset(nafld3, event=="dyslipidemia"), id=id,
                  lipid = tdc(days), e3= cumevent(days))
> ndata <- tmerge(ndata, subset(nafld3, event %in% c("diabetes", "htn",
                                                     "dyslipidemia")),
                  id=id, comorbid= cumevent(days))
> summary(ndata)
Call:
tmerge(data1 = ndata, data2 = subset(nafld3, event %in% c("diabetes",
    "htn", "dyslipidemia")), id = id, comorbid = cumevent(days))

          early late gap within boundary leading trailing tied missid
death         0    0   0      0        0       0    17549    0      0
nafld         0   13   0    318        0    3533        0    0      0
diabetes   2393    0   0   1058        0       1        0    0      0
e1         2393    0   0      0     1058       1        0    0      0
htn        5022    0   0   2045       24       1        5    0      0
e2         5022    0   0      0     2069       1        5    0      0
lipid      8663    0   0   1713       82       2        2    0      0
e3         8663    0   0      0     1795       2        2    0      0
comorbid  16078    0   0      0     4922       4        7  575      0
```

The summary function tells us a lot about the creation process. Each addition of a new endpoint or covariate to the data generates one row in the table. Column labels are explained by figure ??.

- There are 17549 last fu/death additions, which by definition fall at the trailing end of a subject's observation interval: they define the interval.

- There are 13 nafld splits that fall after the end of follow-up ('late'). These are subjects whose first NAFLD fell within a year of the end of their time line, and the one year delay for "confirmed" pushed them over the end. (The time value in the `nafld3` data set is 1 year after the actual notice of NAFLD; no other endpoints have this offset added). The time dependent covariate `nafld` never turns from 0 to 1 for these subjects. (Why were these subjects not removed earlier by my "at least 7 days of follow-up" rule? They are all controls for someone else and so appear in the data at a younger age than their NAFLD date.)

- 318 subjects have a NAFLD diagnosis between time 0 and last follow-up. These are subjects who were selected as matched controls for another NAFLD case at a particular age, and later were diagnosed with NAFLD themselves.

- 2393 of the diabetes diagnoses are before entry, i.e., these are the prevalent cases. One diagnosis occurred on the day of entry ("leading"), and will not be counted as a post-enrollment endpoint, all the other fall somewhere between study entry and last follow-up.

- Conversely, 5 subjects were diagnosed with hypertension at their final visit ("trailing"). These will be counted as an occurrence of a hypertension event (`e2`), but the time dependent covariate `htn` will never become 1.

- 575 of the total comorbidity counts are tied. These are subjects for whom the first diagnosis of 2 of the 3 conditions happened on the same office visit, the cumulative count will jump by 2. (We will see below that 4 subjects had all 3 on the same day.) Many times ties indicate a data error.

Such a detailed look at data set construction may seem over zealous. Our experience is that issues with covariate and event timing occur in nearly all data sets, large or small. The 13 NAFLD cases "after last follow-up" were for instance both a surprise and a puzzle to us; but we have learned through experience that it is best not to proceed until such puzzles are understood. (This particular one was benign.) If, for instance, some condition is noted at autopsy, do we want the related time dependent covariate to change before or after the death event? Some sort of decision has to be made, and it is better to look and understand than to blindly accept an arbitrary programming default.

3.4.2 Fits

Create the covariates for current state and the analysis endpoint. It is important that data manipulations like this occur *after* the final `tmerge` call. Successive `tmerge` calls keep track of the time scale, time-dependent and event covariates, passing the information forward from call to call, but this information is lost when the resulting data frame is manipulated. (The loss is intentional: we won't know if one of the tracked variables has changed.)

The `tmerge` call above used the cumevent verb to count comorbidities, and the first line below verifies that no subject had diabetes, for instance, coded more than once. For this analysis we think of the three conditions as one-time outcomes, you can't get diabetes twice. When the outcome data set is the result of electronic capture one could easily have a diabetes code at every visit, in which case the cumulative count of all events would not be the total number of distinct comorbidities. In this particular data set the diabetes codes had already been preprocessed so

that the data set contains only the first diabetes diagnosis, and likewise with hypertension and dyslipidemia. (In counterpoint, the nafld3 data set has multiple myocardial infarctions for some subjects, since MI can happen more than once.)

```
> with(ndata, if (any(e1>1 | e2>1 | e3>1)) stop("multiple events"))
> ndata$cstate <- with(ndata, factor(diabetes + htn + lipid, 0:3,
                                     c("0mc", "1mc", "2mc", "3mc")))
> temp <- with(ndata, ifelse(death, 4, comorbid))
> ndata$event <- factor(temp, 0:4,
          c("censored", "1mc", "2mc", "3mc", "death"))
> ndata$age1 <- ndata$age + ndata$tstart/365.25   # analysis on age scale
> ndata$age2 <- ndata$age + ndata$tstop/365.25
> check1 <- survcheck(Surv(age1, age2, event) ~ nafld + male, data=ndata,
                      id=id, istate=cstate)
> check1
Call:
survcheck(formula = Surv(age1, age2, event) ~ nafld + male, data = ndata,
    id = id, istate = cstate)

Unique identifiers       Observations        Transitions
             17549              22683               6186

Transitions table:
       to
from     1mc  2mc  3mc death (censored)
  0mc   1829   70    4   263       5705
  1mc      0 1843   28   243       4567
  2mc      0    0 1048   417       3687
  3mc      0    0    0   441       2220
  death    0    0    0     0          0

Number of subjects with 0, 1, ... transitions to each state:
       count
state       0    1   2   3  4
  1mc   15720 1829   0   0  0
  2mc   15636 1913   0   0  0
  3mc   16469 1080   0   0  0
  death 16185 1364   0   0  0
  (any) 12733 3673 938 183 22
```

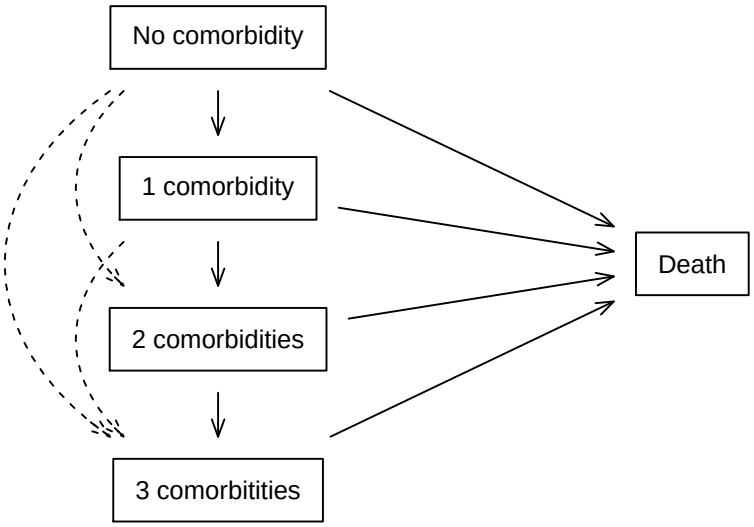
This is a rich data set with a large number of transitions: over 1/4 of the participants have at least one event, and there are 22 subjects who transition through all 5 possible states (4 transitions). Unlike prior examples, subjects do not all enter the study in the same state; about 14% have diabetes at the time of recruitment, for instance. Note one major difference between current state and outcome, namely that the current state endures across intervals: it is based on `tdc` variables while the outcome is based on `event` operators. If a subject has time-dependent

covariates, there may be intermediate intervals where a covariate changed but an outcome did not occur; current state will endure across intervals but the intermediate outcome will be "censor".

We see a number of subjects who "jump" states, e.g., directly from 0 to 2 comorbidities. This serves to remind us that this is actually a model of time until *detected* comorbidity; which will often have such jumps even if the underlying biology is continuous. The data look like the figure below, where the dotted lines are transformations that we observe, but would not be present if the subjects were monitored continuously. A call to the `survcheck` routine is almost mandatory for a complex setup like this, to ensure that the data set which has been built is what you intended to build.

Calling `survcheck` with ~1 on the right hand side or with the covariates for the model on the right hand side will potentially give different event counts, due to the removal of rows with a missing value. Both can be useful summaries. For a multi-state coxph model neither may be exactly correct, however. If the model contains a covariate which applies only to certain transitions, then events that do not depend on that covariate will be retained, while event occurences that do depend on the covariate will be dropped, leading to counts that may be intermediate between the two survcheck outputs.

```
> states <- c("No comorbidity", "1 comorbidity", "2 comorbidities",
              "3 comorbitities", "Death")
> cmat <- matrix(0, 5,5)
> cmat[,5] <- 1
> cmat[1,2] <- cmat[2,3] <- cmat[3,4] <- 1
> cmat[1,3] <- cmat[2,4] <- 1.6
> cmat[1,4] <- 1.6
> dimnames(cmat) <- list(states, states)
> statefig(cbind(4,1), cmat, alty=c(1,2,1,2,2,1,1,1,1,1,1))
```



Since age is the dominant driver of the transitions we have chosen to do the fits directly on age scale rather than model the age effect. We force common coefficients for the transitions from 0 comorbidities to 1, 2 or 3, and for transitions from 1 comorbidity to 2 or 3. This is essentially a model of "any progression" from a given state. We also force the effect of male sex to be the same for any transition to death.

```
> nfit1 <- coxph(list(Surv(age1, age2, event) ~ nafld + male,
                      "0mc":state("1mc", "2mc", "3mc") ~ nafld+ male / common,
                       2:3 + 2:4   ~ nafld + male / common,
                       0:"death" ~ male / common),
                 data=ndata, id=id, istate=cstate)
> nfit1$states
[1] "0mc"   "1mc"   "2mc"   "3mc"   "death"
> nfit1$cmap
      1:2 1:3 2:3 1:4 2:4 3:4 1:5 2:5 3:5 4:5
nafld   1   1   3   1   3   5   7   9  10  11
male    2   2   4   2   4   6   8   8   8   8
```

A list has been used as the formula for the `coxph` call. The first element is a standard formula, and will be the default for all of the transitions found in the model. Elements 2–4 of the list are pseudo formulas, which specify a set of states on the left and covariates on the right, along with the optional modifier `/common`. As shown, there are multiple ways to specify a set of transitions

either by name or by number, the value 0 is shorthand for "any state". The coefficient matrix reveals that the 1:2, 1:3, and 1:4 transitions all share the same coefficients, as intended.

The actual coefficient vector (`coef(fit)`) and variance covariance matrix do not have repeats. The fit also includes a `cmap` component that records the mapping between the coefficient vector and the state transtitions. The result of `coef(nfit1)` is a vector of length 9, the first element of which is the nafld effect for transitions 1:2, 1:3, and 1:4, the second coefficient is the effect of male on those three transitions, etc. Because the coefficient vector, variance matrix, and etc. are identical to those for a simple coxph call, downstream operations such as `predict` and `summary` are unchanged.

The standard printouts makes use of `cmap` to rearrange the output into a nicer format. It is interesting, though not surprising, that the impact of NAFLD on death is largest for those with 0mc and smallest for those with 3mc.

```
> print(coef(nfit1), digits=3)
nafld_1:2  male_1:2 nafld_2:3  male_2:3 nafld_3:4  male_3:4 nafld_1:5
   0.9147    0.1790    0.5208    0.2456    0.4849    0.1490    0.6299
 male_1:5 nafld_2:5 nafld_3:5 nafld_4:5
   0.3293    0.5343    0.5512    0.0722
> print(coef(nfit1, matrix=TRUE), digits=3)  # alternate form
        1:2   1:3   2:3   1:4   2:4   3:4   1:5   2:5   3:5    4:5
nafld 0.915 0.915 0.521 0.915 0.521 0.485 0.630 0.534 0.551 0.0722
male  0.179 0.179 0.246 0.179 0.246 0.149 0.329 0.329 0.329 0.3293
attr(,"states")
[1] "0mc"   "1mc"   "2mc"   "3mc"   "death"
> print(nfit1)
Call:
coxph(formula = list(Surv(age1, age2, event) ~ nafld + male,
    "0mc":state("1mc", "2mc", "3mc") ~ nafld + male/common, 2:3 +
        2:4 ~ nafld + male/common, 0:"death" ~ male/common),
    data = ndata, id = id, istate = cstate)


1:2, 1:3, 1:4    coef exp(coef) se(coef) robust se      z        p
        nafld 0.91468   2.49598  0.06267   0.06737 13.578  < 2e-16
        male  0.17895   1.19596  0.04625   0.04822  3.711 0.000206


2:3, 2:4    coef exp(coef) se(coef) robust se     z       p
   nafld 0.52076   1.68331  0.05227   0.05584 9.327 < 2e-16
   male  0.24559   1.27838  0.04702   0.04991 4.921 8.6e-07


3:4        coef exp(coef) se(coef) robust se     z        p
  nafld 0.48494   1.62408  0.06498   0.06788 7.145 9.02e-13
  male  0.14900   1.16067  0.06250   0.06506 2.290    0.022
```

```
1:5        coef exp(coef) se(coef) robust se     z        p
  nafld 0.62990   1.87742  0.22590   0.22793 2.764  0.00572
  male  0.32935   1.39006  0.05488   0.05466 6.026 1.69e-09


2:5        coef exp(coef) se(coef) robust se     z        p
  nafld 0.53433   1.70630  0.15483   0.14971 3.569 0.000358
  male  0.32935   1.39006  0.05488   0.05466 6.026 1.69e-09


3:5        coef exp(coef) se(coef) robust se     z        p
  nafld 0.55116   1.73526  0.10585   0.10695 5.153 2.56e-07
  male  0.32935   1.39006  0.05488   0.05466 6.026 1.69e-09


4:5        coef exp(coef) se(coef) robust se     z        p
  nafld 0.07225   1.07492  0.09929   0.09908 0.729    0.466
  male  0.32935   1.39006  0.05488   0.05466 6.026 1.69e-09

 States:  1= 0mc, 2= 1mc, 3= 2mc, 4= 3mc, 5= death

Likelihood ratio test=448.4  on 11 df, p=< 2.2e-16
n= 22683, number of events= 6186
```

The summary command does not rearrange.

```
> options(show.signif.stars = FALSE) # display statistical maturity
> summary(nfit1, digits=3)
Call:
coxph(formula = list(Surv(age1, age2, event) ~ nafld + male,
    "0mc":state("1mc", "2mc", "3mc") ~ nafld + male/common, 2:3 +
        2:4 ~ nafld + male/common, 0:"death" ~ male/common),
    data = ndata, id = id, istate = cstate)

  n= 22683, number of events= 6186

             coef exp(coef) se(coef) robust se      z Pr(>|z|)
nafld_1:2 0.91468   2.49598  0.06267   0.06737 13.578  < 2e-16
male_1:2  0.17895   1.19596  0.04625   0.04822  3.711 0.000206
nafld_2:3 0.52076   1.68331  0.05227   0.05584  9.327  < 2e-16
male_2:3  0.24559   1.27838  0.04702   0.04991  4.921 8.60e-07
nafld_3:4 0.48494   1.62408  0.06498   0.06788  7.145 9.02e-13
male_3:4  0.14900   1.16067  0.06250   0.06506  2.290 0.022020
nafld_1:5 0.62990   1.87742  0.22590   0.22793  2.764 0.005717
```

```
male_1:5  0.32935   1.39006  0.05488   0.05466  6.026 1.69e-09
nafld_2:5 0.53433   1.70630  0.15483   0.14971  3.569 0.000358
nafld_3:5 0.55116   1.73526  0.10585   0.10695  5.153 2.56e-07
nafld_4:5 0.07225   1.07492  0.09929   0.09908  0.729 0.465891

          exp(coef) exp(-coef) lower .95 upper .95
nafld_1:2     2.496     0.4006    2.1872     2.848
male_1:2      1.196     0.8361    1.0881     1.315
nafld_2:3     1.683     0.5941    1.5088     1.878
male_2:3      1.278     0.7822    1.1593     1.410
nafld_3:4     1.624     0.6157    1.4218     1.855
male_3:4      1.161     0.8616    1.0217     1.319
nafld_1:5     1.877     0.5326    1.2010     2.935
male_1:5      1.390     0.7194    1.2488     1.547
nafld_2:5     1.706     0.5861    1.2724     2.288
nafld_3:5     1.735     0.5763    1.4071     2.140
nafld_4:5     1.075     0.9303    0.8852     1.305

Concordance= 0.569  (se = 0.004 )
Likelihood ratio test= 448.4  on 11 df,   p=<2e-16
Wald test            = 436.2  on 11 df,   p=<2e-16
Score (logrank) test = 520.2  on 11 df,   p=<2e-16,   Robust = 326.7  p=<2e-16

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

The names attached to the coefficients in a multi-state model are a compromise, designed to give some information to the reader, albeit imperfect. If a variable such as 'sex' only applies to a single coefficient, the simple name is used, even if the coefficient corresponds to multiple transitions. Otherwise a suffix "_a:b" is appended where a:b corresponds to the first transition that maps onto this coefficient. (First in the sense of standard R matrices, i.e., reading the elements of `cmap` in column order.)

A second available keyword is `shared`, which indicates that the baseline hazards for transitions share a common shape. Here is an example:

```
> nfit2 <- coxph(list(Surv(age1, age2, event) ~ nafld + male,
                      "0mc":state("1mc", "2mc", "3mc") ~ nafld+ male / common,
                       2:3 + 2:4   ~ nafld + male / common,
                       1:5 + 2:5 +3:5 ~ male / common + shared),
                  data=ndata, id=id, istate=cstate)
> nfit2$cmap
        1:2 1:3 2:3 1:4 2:4 3:4 1:5 2:5 3:5 4:5
nafld     1   1   3   1   3   5   7   9  10  11
male      2   2   4   2   4   6   8   8   8  12
ph(1:5)   0   0   0   0   0   0   0  13  14   0
```

3.4.3 Timeline data

The `survfit` and `coxph` routines also accept data in what we refer to as a "timeline" form. (The option is still under development so detail may change.) Timeline data contains a case identifier and a timeline variable, where this value pair that is unique for each row. The other covariates are any number of variables whose value is "what was observed at that time", or missing if there was no observation of that variable at that time. In contrast to counting process data, there are no time intervals and no distinction between covariates and endpoints. In this sense the data is much more straightforward; a simple description of what was seen.

Here is a simple example using the mgus2 data set for a competing risks analysis. The `Surv2` operation on the left-hand side indicates to the routine that timeline data is being used.

```
> ctime <- with(mgus2, ifelse(pstat==1, ptime, futime))
> cstat <- with(mgus2, ifelse(pstat==1, 1, 2*death))
> cstat <- factor(cstat, 0:2, c("censor", "PCM", "death"))
> tdata <- data.frame(id=mgus2$id, days=ctime, cstat=cstat)
> # counting process
> mdata1 <- tmerge(mgus2[,1:7], tdata, id, state=event(days, cstat))
> mfit1 <- coxph(Surv(tstart, tstop, state) ~ age + sex, id=id, mdata1)
> # timeline
> mdata2 <- data.frame(mgus2[,1:7], days=0)
> mdata2 <- merge(mdata2, tdata, all=TRUE)
> mfit2 <-  coxph(Surv2(days, cstat) ~ age + sex, id=id, mdata2)
> all.equal(coef(mfit1), coef(mfit2))
[1] TRUE
```

The counting process data set from `tmerge` as fewer rows but a more complex structure.

```
> mdata1[1:3,]
  id age sex dxyr  hgb creat mspike tstart tstop state
1  1  88   F 1981 13.1   1.3    0.5      0    30 death
2  2  78   F 1968 11.5   1.2    2.0      0    25 death
3  3  94   M 1980 10.5   1.5    2.6      0    46 death
> print(mdata2[1:6,], na.print='.')
  id days age sex dxyr  hgb creat mspike cstat
1  1    0  88   F 1981 13.1   1.3    0.5     .
2  1   30  NA   .   NA   NA    NA     NA death
3  2    0  78   F 1968 11.5   1.2    2.0     .
4  2   25  NA   .   NA   NA    NA     NA death
5  3    0  94   M 1980 10.5   1.5    2.6     .
6  3   46  NA   .   NA   NA    NA     NA death
```

Here is a reprise of the NAFLD data set using the timeline form.

```
> tldata <- data.frame(nafld1[,1:7],
                       days= 0,  death=0, iage=nafld1$age, nafld=0)
> tldata <- merge(tldata, with(nafld1, data.frame(id=id, days=futime, death=status)),
```

```
                all=TRUE)
> # Add in the comorbidities of interest.  None of these 4 happen to have
> #  duplicates (MI does, for instance).
> # Start by removing the the 13 rows with a "confirmed NAFLD" (actual NAFLD + 1 year)
> #  that is after the actual last follow-up date.
> # Treat diabetes before day 0 as diabetes on day 0.
> badrow <- which(nafld3$days > nafld1$futime[match(nafld3$id, nafld1$id)])
> fixnf3 <- nafld3[-badrow,]
> tldata <- merge(tldata, with(subset(fixnf3, event=="diabetes"),
                               data.frame(id=id, days=pmax(0,days), diabetes=1)),
                      all=TRUE, by=c("id", "days"))
> tldata <- merge(tldata, with(subset(fixnf3, event=="htn"),
                               data.frame(id=id, days=pmax(0,days), htn=1)),
                        all=TRUE, by=c("id", "days"))
> tldata <- merge(tldata, with(subset(fixnf3, event=="dyslipidemia"),
                               data.frame(id=id, days= pmax(0, days), dyslipid=1)),
                          all=TRUE, by=c("id", "days"))
> tldata <- merge(tldata, with(subset(fixnf3, event=="nafld"),
                               data.frame(id=id, days= pmax(0,days), nafld=1)),
                       by=c("id", "days"), all=TRUE)
> tldata$nafld <- with(tldata, ifelse(is.na(nafld.y), nafld.x, nafld.y))
```

We want to assume that a subject is non-NAFLD until detection, which means setting `nafld` to 0 at time 0; this was done in the first tldata line above. Ideally, we would have a version of `merge` that overwrites that value for a subject with NAFLD on day 0, but that is not how `merge` works; given `any` tied days between tldata and fixnf3 there will be two variables `nafld.x` and `nafld.y`. The last line above makes one from the two. Initial values for the number of comorbidities are handled by the cumevent function.

```
> #
> # For cumulative events within subject we use a helper function
> cumevent <- function(id, time, status, istate) {
      # do all the work on ordered data
      ord <- order(id, time)
      id2 <- id[ord]
      time2 <- time[ord]
      stat2 <- ifelse(is.na(status[ord]), 0, status[ord])
      firstid <- !duplicated(id)
      csum <- cumsum(stat2)
      indx <- match(id2, id2)
      cstat<- csum + stat2[indx] - csum[indx]
      cstat[stat2==0] <- 0

      if (!missing(istate)) cstat[firstid] <- istate

      keep <- (firstid | (!is.na(stat2)& stat2 !=0))
      newdata <- data.frame(id=id2[keep], time=time2[keep], status=cstat[keep])
```

```
      newdata
  }
> temp1 <- rowSums(tldata[,c('diabetes', 'htn', 'dyslipid')], na.rm=TRUE)
> temp2 <- with(tldata, cumevent(id, days, pmax(temp1, 4*death, na.rm=TRUE)))
> state <- factor(pmin(temp2$status, 4), -1:4,
                  c("censor", paste0(0:3, "mc"), "death"))
> tldata <- merge(tldata, data.frame(id=temp2$id, days=temp2$time, state=state),
                all=TRUE)
> tldata$age <- with(tldata, days/365.25 + age[match(id, id)])
> check2 <- survcheck(Surv2(days, state) ~ 1, id=id, tldata)
> check2$transitions
       to
from     1mc  2mc  3mc death (censored)
  0mc   1829   70    4   263       5705
  1mc      0 1843   28   243       4567
  2mc      0    0 1048   417       3687
  3mc      0    0    0   441       2220
  death    0    0    0     0          0
> nfit2 <- coxph(list(Surv2(age, state) ~ nafld + male,
                      "0mc":state("1mc", "2mc", "3mc") ~ nafld+ male / common,
                       2:3 + 2:4   ~ nafld + male / common,
                       0:"death" ~ male / common),
                data=tldata, id=id)
> round(coef(nfit2), 3)
nafld_1:2  male_1:2 nafld_2:3  male_2:3 nafld_3:4  male_3:4 nafld_1:5
    0.915     0.179     0.521     0.246     0.485     0.149     0.630
 male_1:5 nafld_2:5 nafld_3:5 nafld_4:5
    0.329     0.534     0.551     0.072
```

The resulting fit it identical to the one that used the counting process data set.

There are advantages and disadvantages to the timeline data as compared to counting process style.

- Counting process style has been available for a long while — it was first incorporated into the survival package in 1986 — and it has been adopted by several other packages. The format is hence familiar to many users.
- Nevertheless, it contains many traps for the unwary. The distinction between outcome and predictor variables is critical: the former applies at the end of each (time1, time2) interval and the former at the start of the interval. If one is fitting multiple models, one where the number of comorbid conditions was a predictor and one where it is the outcome, different variables and/or data sets are required. In multi-state data sets separate variables are needed for the current state and for an event, and they behave differently.
- The tmerge routine simplifies some tasks, but it can be subtle. The author/maintainers of the routine are often puzzled ourselves. When there are multiple possible endpoints and/or multiple time scales it can get particularly challenging.

- Timeline data is simpler. There is no distinction between covariates and events, or between current and next state. Any necessary temporal orderings are created by the underlying survival models when processing the formula. This makes it easier to get the data set correct.
- Timeline data sets are created using standard tools. The example above used only tools in base R (a restriction for vignettes in the list of 'recommended' packages), but there is a wide range of available data manipulation tools. The result need only obey the requirement of having no duplicate (id, timescale) keys. This is a common constraint in relational databases.

3.5 Testing proportional hazards

The usual Cox model with p covariates has the form

$$\begin{aligned} \lambda(t) &= \lambda_0(t) e^{\beta_1 x_1 + \beta_2 x_2 + \ldots + \beta_p x_p} \\ &= e^{\beta_0(t) + \beta_1 x_1 + \beta_2 x_2 + \ldots + \beta_p x_p} \end{aligned}$$

A key simplifying assumption of the model is that all of the coefficients except β_0 (the baseline hazard) are constant over time, which is referred to as the *proportional hazards* assumption. Numerous approaches to verifying or testing this assumption have been proposed, of which the three most enduring have been the addition of an additional constructed covariate, score tests, and tests based on cumulative martingale sums. Each of these is normally applied to one covariate at a time.

3.5.1 Constructed variables

For the constructed variable approach, assume that the true form of the model for variable x_1 is $\beta_1(t)x_1$, with the coefficient having the simple linear form $\beta_1(t) = a + bt$. Then

$$\begin{aligned} \beta_1(t)x_1 &= ax_1 + b(x_1 t) \\ &= ax_1 + bz \end{aligned} \tag{3.4}$$

that is, we can create a special time-dependent covariate $z = x_1 t$, add add it to the data set, and then use an ordinary `coxph` fit.

Consider the veterans lung cancer data set, which has often been used to illustrate non-proportional hazards. Adding this special covariate is not quite as simple as writing

```
> fit2 <- coxph(Surv(time, status) ~ trt + trt*time + celltype + karno,
                data = veteran)
```

The problem is that `time` is trying to play two roles in the above equation, the *final* follow-up time for each subject (the left hand side of the formula) and the *continuous* time scale t of equation (3.4). The `veteran` data set contains the first of these as an explicit variable, and the `coxph` function will use that variable on both the right and left hand sides, which is not the desired time-dependent effect. The solution to to create the special variable, explicitly, before calling the regression function. Since the Cox model adds a term to the likelihood at each unique death time, it is sufficient to create a data set with the same granularity.

```
> dtime <- unique(veteran$time[veteran$status==1]) # unique times
> newdata <- survSplit(Surv(time, status) ~ trt + celltype + karno,
                       data=veteran, cut=dtime)
> nrow(veteran)
[1] 137
> nrow(newdata)
[1] 5959
> fit0 <- coxph(Surv(time, status) ~ trt + celltype + karno, veteran)
> fit1 <- coxph(Surv(tstart, time, status) ~ trt + celltype + karno,
                data=newdata)
> fit2 <- coxph(Surv(tstart, time, status) ~ trt + celltype + karno +
                time:karno, newdata)
> fit2
Call:
coxph(formula = Surv(tstart, time, status) ~ trt + celltype +
    karno + time:karno, data = newdata)

                       coef  exp(coef)   se(coef)      z        p
trt                1.686e-01  1.184e+00  2.048e-01  0.823  0.41034
celltypesmallcell  8.990e-01  2.457e+00  2.746e-01  3.274  0.00106
celltypeadeno      1.192e+00  3.293e+00  2.991e-01  3.985 6.74e-05
celltypelarge      4.034e-01  1.497e+00  2.833e-01  1.424  0.15454
karno             -4.015e-02  9.606e-01  6.383e-03 -6.291 3.16e-10
karno:time         1.110e-04  1.000e+00  4.688e-05  2.369  0.01784

Likelihood ratio test=66.92  on 6 df, p=1.75e-12
n= 5959, number of events= 128
> fit2b <- coxph(Surv(tstart, time, status) ~ trt + celltype + karno +
                rank(time):karno, newdata)
```

The fits give a warning message about the use of the `time` variable on both sides of the equation, since two common cases where time appears on both sides are the naive model shown further above and frank typing mistakes. In this particular case we can ignore the warning since the data set was carefully constructed for this special purpose, but it should never be treated casually.

Alternatively, `coxph` has built-in functionality that will build the expanded data set for us, behind the scenes, and then use that expanded data for the fit. Here is eqivalent code to test the Karnofsky variable:

```
> fit2 <- coxph(Surv(tstart, time, status) ~ trt + celltype + karno +
                tt(karno), data =newdata,
                tt = function(x, t,...) x*t)
```

There are 4 issues with the constructed variable approach.

1. The choice $\beta(t) \approx a + bt$ was arbitrary. Perhaps the true form is $a + b\log(t)$ (fit2b above), or some other function.

2. The intermediate data set can become huge. It will be of order $O(nd)$ where d is the number of unique event times, and d grows along with n.

3. The coefficients for a factor variable such as celltype can be confusing, since the results depend on how the 0/1 indicators for the variable are chosen.

4. Outliers in time are an issue. The veteran cancer data set, for instance, contains a time of 999 days (a particularly suspicious value in any data set). The Cox model itself depends only on the rank order of the event times, so such outliers are not an issue for the base model, but as a covariate these values can have undue influence. The time-dependent coeffient for Karnofsky has $p < .01$ in fit2b above, which uses rank(time), a change that is largely due to dampening the leverage of outliers.

3.5.2 Score tests

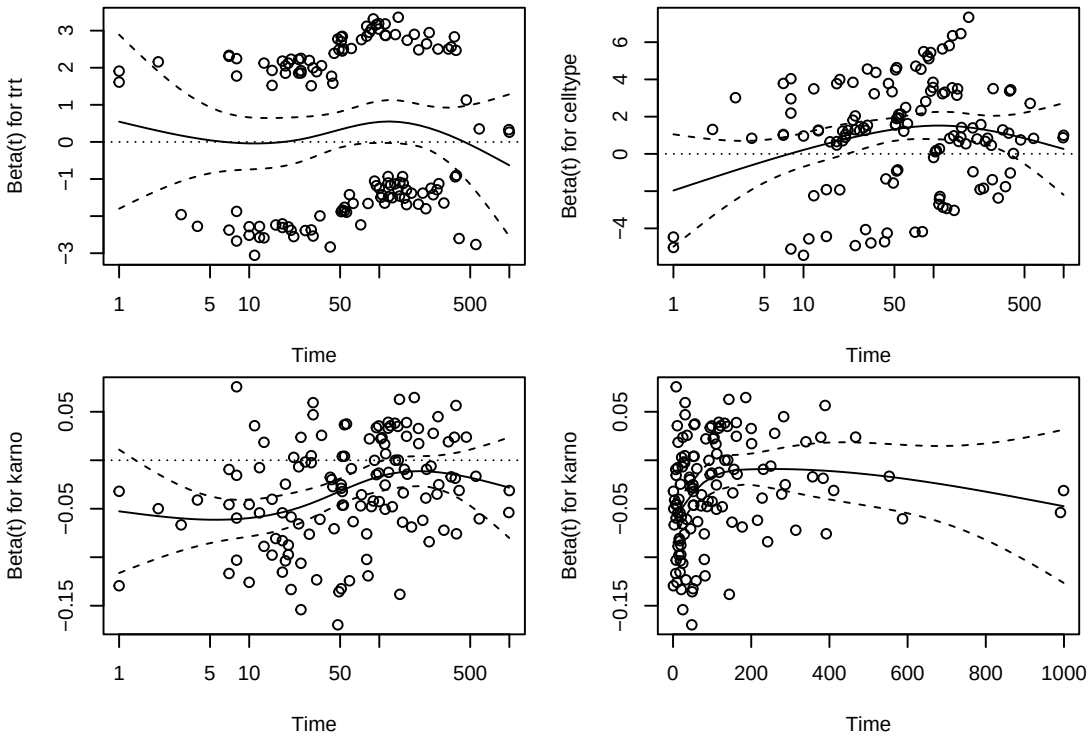
The `cox.zph` function checks proportional hazards for a fitted Cox model directly, and tries to address the four issues discussed above.

- It is easy to specify alternate time transforms such as x*log(t). More importantly, the code produces both a diagnostic plot that suggests the shape of any non-proportionality, along with a test of the chosen time-transform.
- The test statistic is based on a score test, which does not require creating the expanded data set.
- Multi-covariate terms such as a factor or splines are by default treated as a single effect.
- The default time transform is designed to minimize outliers in time.

Shown below are results for the veterans data using `fit0` from above. The score statistic for the simple term x*time (`zp1`) closely matches the Wald test for the full time dependent fit found in `fit2` above, which is what we would expect; score, Wald and likelihood ratio tests usually agree quite closely for Cox models.

```
> zp0 <- cox.zph(fit0, transform='identity')
> zp0
            chisq df       p
trt       0.00493  1 0.94402
celltype 18.41391  3 0.00036
karno     6.05160  1 0.01389
GLOBAL   20.87086  5 0.00086
> zp1 <- cox.zph(fit0, transform='log')
> zp1
           chisq df       p
trt        0.215  1 0.64298
celltype 13.586  3 0.00353
karno    10.079  1 0.00150
GLOBAL   21.451  5 0.00067
```

```
> oldpar <- par(mfrow=c(2,2))
> for (i in 1:3) {plot(zp1[i]); abline(0,0, lty=3)}
> plot(zp0[3])
> par(oldpar)
```



A test for zero slope, from a least squares regression using data in the matching plot approximates the score test. (In versions of the package prior to survival3.0, the approximate test was used for the formal test and printout as well.) If proporitional hazard holds we would expect the fitted line to be horizontal, i.e., $\beta(t)$ is constant. Rather than show a fitted line the plot adds a general smooth curve, which can help reveal the *form* of non-proportional hazards, if it exists. The first three panels of the plot show curves for the three covariates on a log(time) scale. Since `celltype` is a factor, the plot shows the time dependent effect of the portion of the linear predictor associated with cell type; if proportional hazards is true wrt that term a fitted line should be horizontal with a coefficient of 1. The effect of Karnofsky score appears to become essentially 0 after approximately 6 months; for this cohort of subjects with advanced lung cancer, a 6 month old assessment of Karnofsky is no longer relevant. The corresponding plot in the lower right panel, however, shows that the outlier time of 999 days has an undue influence on any such regression. A test of proportional hazards on that scale must also be treated with caution. The plot using log scale lacks these outliers and is more interpretable.

The default time transform is based on a Kaplan-Meier transform, i.e., that monotone transform of the time axis that will cause the KM plot to be a straight line. This is a good default for the score tests, since it essentially guarrantees that there wil be no outliers in the constructed $xg(time)$ variable, while dealing with censoring in a defensible way. That is, the code has opted

for a *safe* default. It is not as easily interpreted as other scales for the plots, however.

The `cox.zph` function does not attempt a score test for random effects (frailty) terms, in fact is not clear what the computation for such a test should be. The function will check other covariates in a model that contains a random effect, however; in that test the estimated random effect per subject is essentially treated as a fixed offset.

3.5.3 Computational details

The score test is simple in theory, but "the devil is in the details" as they say. Consider adding the constructed variables for celltype to the fit. That is g(t)*x2, g(t)*x3, g(t)*x4, where x2-x4 are the three dummy variables that represent celltype. The new model has 5 + 3 covariates, and is evaluated at $(\hat{\beta}, 0, 0, 0)$. The score statistic at this coefficient value will be $(0, 0, 0, 0, 0, u_6, u_7, u_8)$, the first 5 elements are zero since that is the definition of model convergence for $\hat{\beta}$.

The information or Hessian matrix for a Cox model is

$$\sum_{j \in deaths} V(t_j) = \sum_j V_j$$

where V_j is the variance matrix of the weighted covariate values, over all subjects at risk at time t_j. Then the expanded information matrix for the score test is

$$\begin{aligned} H &= \begin{pmatrix} H_1 & H_2 \\ H_2' & H_3 \end{pmatrix} \\ H_1 &= \sum V(t_j) \\ H_2 &= \sum V(t_j) g(t_j) \\ H_3 &= \sum V(t_j) g^2(t_j) \end{aligned}$$

The inverse of the matrix will be more numerically stable if $g(t)$ is centered at zero, and this does not change the test statistic. In the usual case $V(t)$ is close to constant in time — the variance of X does not change rapidly — and then H_2 is approximately zero. The original cox.zph used an approximation, which is to assume that $V(t)$ is exactly constant. In that case $H_2 = 0$ and $H_3 = \sum V(t_j) \sum g^2(t_j)$ and the test is particularly easy to compute. This assumption of identical components can fail badly for models with a covariate by strata interaction, and for some models with covariate dependent censoring.

If there are p covariates, the new score vector will be of length $2p$ and the information matrix will be $2p$ by $2p$. These can be computed using a simple variant of the C code for coxph; no iteration is done. In fact, the use of time-weighted risk sets has been proposed by several authors, for multiple rationales. This has not been implemented in the coxph routine (but we have thought about it).

The score tests are done for single covariates or terms. Using the veteran example, a test for celltype as a term would first select rows 1-5 and 7-9 of the score vector U and information matrix H; i.e., if `j <- c(1:5, 7:9)` the test is `U[j] %*% inverse(H[j,j]) %*% U[j]`. (This is done using the the `solve` function of course, rather than taking an explicit inverse). The result is a 3 degree of freedom chisquare statistic. For a single variable test, the fact that only a single element of `U[j]` is non-zero allows for a faster shortcut calculation.

A few further things need to be considered.

1. There may be NA coefficients in the fit, e.g., for a model that has redundant variables in its X matrix. It is fairly simple to keep track of these, and remove any such from our set of variables j.

2. There is not a good defintion of how to test PH for a random effects term, e.g., from a coxme model or a copxh fit with a frailty term. For these, we treat the resultant random coefficients as though they were fixed, and test the other variable under this constraint.

3. For a penalized model, the penalty is assumed to apply to both the original and to then extended coefficients. However,

   - Penalties depend only the coefficient $hat\beta$, not on the data or the time weights.
   - All the penalties that we support are 0 at $\beta = 0$, and have a first derivative of 0 there, so there is no impact on the score vector U. U is 0 for the current covariates, by definition, and the new ones are being evaluated at 0.
   - There will be an impact on the second derivative, however. But this will by definition be idential to the penalty for the original variables.

4. The most difficult issue is use of a robust variance in the original model. This requires not just the score vector U, but the *nbyp* matrix of of dfbeta residuals D. This requires a special version of the relevant C routine; there are no simple computaional shortcuts.

Chapter 4

Accelerated Failure Time models

4.1 Usage

The survreg function implements the class of parametric accelerated failure time models. Assume that the survival time y satisfies $\log(y) = X'\beta + \sigma W$, for W from some given distribution. Then if $\Lambda_w(t)$ is the cumulative hazard function for W, the cumulative hazard function for subject i is $\Lambda_w[\exp(-\eta_i/\sigma)t]$, that is, the time scale for the subject is accelerated by a constant factor. A good description of the models is found in chapter 3 of Kalbfleisch and Prentice [4].

The following fits a Weibull model to the lung cancer data set included in the package.

```
> fit <- survreg(Surv(time, status) {\twiddle} age + sex + ph.karno, data=lung,
        dist='weibull')
> fit
Call:
survreg(formula = Surv(time, status) {\twiddle} age + sex + ph.karno, data = lung, dist
         = "weibull")

Coefficients:
 (Intercept)          age       sex    ph.karno
    5.326344 -0.008910282 0.3701786 0.009263843

Scale= 0.7551354

Loglik(model)= -1138.7   Loglik(intercept only)= -1147.5
        Chisq= 17.59 on 3 degrees of freedom, p= 0.00053
n=227 (1 observations deleted due to missing)
```

The code for the routines has undergone substantial revision between releases 4 and 5 of the code. Calls to the older version are not compatable with all of the changes, users can use the survreg.old function if desired, which retains the old argument style (but uses the newer maximization code). Major additions included penalzed models, strata, user specified distributions, and more stable maximization code.

4.2 Strata

In a Cox model the `strata` statement is used to allow separate baseline hazards for subgroups of the data, while retaining common coefficients for the other covariates across groups. For parametric models, the statement allows for a separate scale parameter for each subgroup, but again keeping the other coefficients common across groups. For instance, assume that separate "baseline" hazards were desired for males and females in the lung cancer data set. If we think of the intercept and scale as the baseline shape, then an appropriate model is

```
> sfit <- survreg(Surv(time, status) ~ sex + age + ph.karno + strata(sex),
        data=lung)
> sfit
Coefficients:
 (Intercept)       sex          age   ph.karno
   5.059089 0.3566277 -0.006808082 0.01094966

Scale:
     sex=1     sex=2
 0.8165161 0.6222807

Loglik(model)= -1136.7   Loglik(intercept only)= -1146.2
        Chisq= 18.95 on 3 degrees of freedom, p= 0.00028
```

The intercept only model used for the likelihood ratio test has 3 degrees of freedom, corresponding to the intercept and two scales, as compared to the 6 degrees of freedom for the full model.

This is quite different from the effect of the `strata` statement in `censorReg`; there it acts as a 'by' statement and causes a totally separate model to be fit to each gender. The same fit (but not as nice a printout) can be obtained from `survreg` by adding an explicit interaction to the formula:

```
Surv(time,status) ~ sex + (age + ph.karno)*strata(sex)
```

4.3 Penalized models

Let the linear predictor for a `survreg` model be $\eta = X\beta + Z\omega$, and consider maximizing the penalized log-likelihood

$$PLL = LL(y; \beta, \omega) - p(\omega; \theta)\,,$$

where β and ω are the unconstrained effects, respectively, X and Z are the covariates, p is a function that penalizes certain choices for ω, and θ is a vector of tuning parameters.

For instance, ridge regression is based on the penalty $p = \theta \sum \omega_j^2$; it shrinks coefficients towards zero.

The penalty functions in `survreg` currently use the same code as those for `coxph`. This works well in the case of ridge and pspline, but frailty terms are more problematic in that the code to automatically choose the tuning parameter for the random effect no longer solves an MLE equation. The current code will not lead to the correct choice of penalty.

4.4 Specifying a distribution

The fitting routine is quite general, and can accept any distribution that spans the real line for W, and any monotone transformation of y. The standard set of distributions is contained in a list `survreg.distributions`. Elements of the list are of two types. Basic elements are a description of a distribution. Here is the entry for the logistic family:

```
logistic = list(
    name  = "Logistic",
    variance = function(parm) pi^2/3,
    init  = function(x, weights, ...) \{
        mean <- sum(x*weights)/ sum(weights)
        var  <- sum(weights*(x-mean)^2)/ sum(weights)
        c(mean, var/3.2)
        \},
    deviance= function(y, scale, parms) \{
        status <- y[,ncol(y)]
        width <- ifelse(status==3,(y[,2] - y[,1])/scale, 0)
        center <- y[,1] - width/2
        temp2 <- ifelse(status==3, exp(width/2), 2) #avoid a log(0) message
        temp3 <- log((temp2-1)/(temp2+1))
        best <- ifelse(status==1, -log(4*scale),
                                  ifelse(status==3, temp3, 0))
        list(center=center, loglik=best)
        \},
    density = function(x, ...) \{
        w <- exp(x)
        cbind(w/(1+w), 1/(1+w), w/(1+w)^2, (1-w)/(1+w), (w*(w-4) +1)/(1+w)^2)
        \},
    quantile = function(p, ...) log(p/(1-p))
    )
```

- Name is used to label the printout.
- Variance contains the variance of the distribution. For distributions with an optional parameter such as the t-distribution, the `parm` argument will contain those parameters.
- Deviance gives a function to compute the deviance residuals. More on this is explained below in the mathematical details.
- The density function gives the necessary quantities to fit the distribution. It should return a matrix with columns $F(x)$, $1 - F(x)$, $f(x)$, $f'(x)/f(x)$ and $f''(x)/f(x)$, where f' and f'' are the first and second derivatives of the density function, respectively.
- The quantiles function returns quantiles, and is used for residuals.

The reason for returning both F and $1 - F$ in the density function is to avoid round off error when $F(x)$ is very close to 1. This is quite simple for symmetric distributions, in the Gaussian

case for instance we use `qnorm(x)` and `qnorm(-x)` respectively. (In the intermediate steps of iteration very large deviates may be generated, and a probabilty value of zero will cause further problems.)

Here is an example of the second type of entry:

```
exponential = list(
    name  = "Exponential",
    dist  = "extreme",
    scale =1 ,
    trans = function(y) log(y),
    dtrans= function(y) 1/y ,
    itrans= function(x) exp(x)
    )
```

This states that an exponential fit is computed by fitting an extreme value distribution to the log transformation of y. (The distribution pointed to must not itself be a pointer to another). The extreme value distribution is restricted to have a scale of 1. The first derivative of the transformation, `dtrans`, is used to adjust the final log-likelihood of the model back to the exponential's scale. The inverse transformation `itrans` is used to create predicted values on the original scale.

The formal rules for an entry are that it must include a name, either the "dist" component or the set "variance","init", "deviance", "density" and "quantile", an optional scale, and either all or none of "trans", "dtrans" and "itrans".

The `dist="weibull"` argument to the `survreg` function chooses the appropriate list from the survreg.distributions object. User defined distributions of either type can be specified by supplying the appropriate list object rather than a character string. Distributions should, in general, be defined on the entire real line. If not the minimizer used is likely to fail, since it has no provision for range restrictions.

Currently supported distributions are

- basic
  - (least) Extreme value
  - Gaussian
  - Logistic
  - t-distribution
- transformations
  - Exponential
  - Weibull
  - Log-normal ('lognormal' or 'loggaussian')
  - Log-logistic ('loglogistic')

4.5 Residuals

4.5.1 Response

The target return value is $y - \hat{y}$, but what should we use for y when the observation is not exact? We will let $\hat{y}_0$ be the MLE for the location parameter μ over a data set with only the observation of interest, with σ fixed at the solution to the problem as a whole, subject to the constraint that μ be consistent with the data. That is, for an observation right censored at $t = 20$, we constain $\mu \geq 20$, similarly for left censoring, and constrain μ to lie within the two endpoints of an interval censored observation. To be consistent as the width of an interval censored observation goes to zero, this definition does require that the mode of the density lies at zero.

For exact, left, and right censored observations $\hat{y}_0 = y$, so that this appears to be an ordinary response residual. For interval censored observations from a symmetric distribution, $\hat{y}_0 =$ the center of the censoring interval. The only unusual case, then, is for a non-symmetric distribution such as the extreme value. As shown later in the detailed information on distributions, for the extreme value distribution this occurs for $\hat{y}_0 = y^l - \log(b/[exp(b) - 1])$, where $b = y^u - y^l$ is the length of the interval.

4.5.2 Deviance

Deviance residuals are response residuals, but transformed to the log-likelihood scale.

$$d_i = sign(r_i)\sqrt{LL(y_i, \hat{y}_0; \sigma) - LL(y_i, \eta_i; \sigma)}$$

The definition for $\hat{y}_0$ used for response residuals, however, could lead to the square root of a negative number for left or right censored observations, e.g., if the predicted value for a right censored observation is less than the censoring time for that observation. For these observations we let $\hat{y}_0$ be the *unconstrained* maximum, which leads to $yhat_0 = -\infty$ and $+\infty$ for right and left censored observations, respectively, and a log-likelihood term of 0.

The advantages of these residuals for plotting and outlier detection are nicely detailed in McCullagh and Nelder [7]. However, unlike GLM models, deviance residuals for interval censored data are not free of the scale parameter. This means that if there are interval censored data values and one fits two models A and B, say, that the sum of the squared deviance residuals for model A minus the sum for model B is *not* equal to the difference in log-likelihoods. This is one reason that the current `survreg` function does not inherit from class `glm`: `glm` models use the deviance as the main summary statistic in the printout.

4.5.3 Dfbeta

The `dfbeta` residuals are a matrix with one row per subject and one column per parameter. The ith row gives the approximate change in the parameter vector due to observation i, i.e., the change in $\hat{\beta}$ when observation i is added to a fit based on all observations but the ith. The `dfbetas` residuals scale each column of this matrix by the standard error of the respective parameter.

4.5.4 Working

As shown in section 4.7 below, the Newton-Raphson iteration used to solve the model can be viewed as an iteratively reweighted least squares problem with a dependent variable of "current prediction - correction". The working residual is the correction term.

4.5.5 Likelihood displacement residuals

Escobar and Meeker [1] define a matrix of likelihood displacement residuals for the accelerated failure time model. The full residual information is a square matrix $\ddot{A}$, with dimension the number of pertubations considered. Three examples are developed in detail, all with dimension n, the number of observations.

Case weight pertubations measure the overall effect on the parameter vector of dropping a case. Let V be the variance matrix of the model, and L the n by p matrix with elements $\partial L_i/\partial\beta_j$, where L_i is the likelihood contribution of the ith observation. Then $\ddot{A} = LVL'$. The residuals function returns the diagonal values of the matrix. Note that LV equals the `dfbeta` residuals.

Response pertubations correspond to a change of 1 σ unit in one of the response values. For a Gaussian linear model, the equivalent computation yields the diagonal elements of the hat matrix.

Shape pertubations measure the effect of a change in the log of the scale parameter by 1 unit.

The `matrix` residual type returns the raw values that can be used to compute these and other LD influence measures. The result is an n by 6 matrix, containing columns for

$$L_i \quad \frac{\partial L_i}{\partial \eta_i} \quad \frac{\partial^2 L_i}{\partial \eta_i^2} \quad \frac{\partial L_i}{\partial \log(\sigma)} \quad \frac{\partial L_i}{\partial \log(\sigma)^2} \quad \frac{\partial^2 L_i}{\partial \eta \partial \log(\sigma)}$$

4.6 Predicted values

4.6.1 Linear predictor and response

The linear predictor is $\eta_i = x_i'\hat{\beta}$, where x_i is the covariate vecor for subject i and $\hat{\beta}$ is the final parameter estimate. The standard error of the linear predictor is $x_i'Vx_i$, where V is the variance matrix for $\hat{\beta}$.

The predicted response is identical to the linear predictor for fits to the untransformed distributions, i.e., the extreme-value, logistic and Gaussian. For transformed distributions such as the Weibull, for which $\log(y)$ is from an extreme value distribution, the linear predictor is on the transformed scale and the response is the inverse transform, e.g. $\exp(\eta_i)$ for the Weibull. The standard error of the transformed response is the standard error of η_i, times the first derivative of the inverse transformation.

4.6.2 Terms

Predictions of type `terms` are useful for examination of terms in the model that expand into multiple dummy variables, such as factors and p-splines. The result is a matrix with one column for each of the terms in the model, along with an optional matrix of standard errors. Here is an example using psplines on the 1980 Stanford data

```
> fit <- survreg(Surv(time, status) ~ pspline(age, df=3) + t5, stanford2,
        dist='lognormal')
> tt <- predict(fit, type='terms', se.fit=T)
> yy <- cbind(tt$fit[,1], tt$fit[,1] -1.96*tt$se.fit[,1],
                          tt$fit[,1] +1.96*tt$se.fit[,1])
> matplot(stanford2$age, yy, type='l', lty=c(1,2,2))

> plot(stanford2$age, stanford2$time, log='y',
        xlab='Age', ylab='Days', ylim=c(.1, 10000))
> matlines(stanford2$age, exp(yy+ attr(tt$fit, 'constant')), lty=c(1,2,2))
```

The second plot puts the fit onto the scale of the data, and thus is similar in scope to figure 1 in Escobar and Meeker [1]. Their plot is for a quadratic fit to age, and without T5 mismatch score in the model.

4.6.3 Quantiles

If predicted quantiles are desired, then the set of probability values p must also be given to the `predict` function. A matrix of n rows and p columns is returned, whose ij element is the p_jth quantile of the predicted survival distribution, based on the covariates of subject i. This can be written as $X\beta + z_q\sigma$ where z_q is the qth quantile of the parent distribution. The variance of the quantile estimate is then cVc' where V is the variance matrix of (β, σ) and $c = (X, z_q)$.

In computing confidence bands for the quantiles, it may be preferable to add standard errors on the untransformed scale. For instance, consider the motor reliability data of Kalbfleisch and Prentice [5].

```
> fit <- survreg(Surv(time, status) ~ temp, data=motors)
> q1 <- predict(fit, data.frame(temp=130), type='quantile',
                p=c(.1, .5, .9), se.fit=T)
> ci1 <- cbind(q1$fit, q1$fit - 1.96*q1$se.fit, q1$fit + 1.96*q1$se.fit)
> dimnames(ci1) <- list(c(.1, .5, .9), c("Estimate", "Lower ci", "Upper ci"))
> round(ci1)
    Estimate Lower ci Upper ci
0.1    15935     9057    22812
0.5    29914    17395    42433
0.9    44687    22731    66643

> q2 <- predict(fit, data.frame(temp=130), type='uquantile',
                p=c(.1, .5, .9), se.fit=T)
> ci2 <- cbind(q2$fit, q2$fit - 1.96*q2$se.fit, q2$fit + 1.96*q2$se.fit)
> ci2 <- exp(ci2)  #convert from log scale to original y
> dimnames(ci2) <- list(c(.1, .5, .9), c("Estimate", "Lower ci", "Upper ci"))
> round(ci2)
    Estimate Lower ci Upper ci
0.1    15935    10349    24535
0.5    29914    19684    45459
0.9    44687    27340    73041
```

Using the (default) Weibull model, the data is fit on the $\log(y)$ scale. The confidence bands obtained by the second method are asymmetric and may be more reasonable. They are also guarranteed to be > 0.

This example reproduces figure 1 of Escobar and Meeker [1].

```
> plot(stanford2$age, stanford2$time, log='y',
       xlab='Age', ylab='Days', ylim=c(.01, 10^6), xlim=c(1,65))
> fit <- survreg(Surv(time, status) ~ age + age^2, stanford2,
       dist='lognormal')
> qq <- predict(fit, newdata=list(age=1:65), type='quantile',
        p=c(.1, .5, .9))
> matlines(1:65, qq, lty=c(1,2,2))
```

Note that the percentile bands on this figure are really quite a different object than the confidence bands on the spline fit. The latter reflect the uncertainty of the fitted estimate and are related to the standard error. The quantile bands reflect the predicted distribution of a subject at each given age (assuming no error in the quadratic estimate of the mean), and are related to the standard deviation of the population.

4.7 Fitting the model

With some care, parametric survival can be written so as to fit into the iteratively reweighted least squares formulation used in Generalized Linear Models of McCullagh and Nelder [7]. A detailed description of this setup for general maximum likelihood computation is found in Green [3].

Let y be the data vector (possibly transformed), and x_i be the vector of covariates for the ith observation. Assume that

$$z_i \equiv \frac{y_i - x_i'\beta}{\sigma} \sim f$$

for some distribution f, where y may be censored.

Then the likelihood for y is

$$l = \left(\prod_{exact} f(z_i)/\sigma\right)\left(\prod_{right}\int_{z_i}^{\infty} f(u)du\right)\left(\prod_{left}\int_{-\infty}^{z_i} f(u)du\right)\left(\prod_{interval}\int_{z_i^l}^{z_i^u} f(u)du\right),$$

where "exact", "right", "left", and "interval" refer to uncensored, right censored, left censored, and interval censored observations, respectively, and z_i^l, z_i^u are the lower and upper endpoints, respectively, for an interval censored observation. Then the log likelihood is defined as

$$LL = \sum_{exact} g_1(z_i) - log(\sigma) + \sum_{right} g_2(z_i) + \sum_{left} g_3(z_i) + \sum_{interval} g_4(z_i, z_i^*)\,, \tag{4.1}$$

where $g_1 = \log(f)$, $g_2 = \log(1-F)$, etc.

Derivatives of the LL with respect to the regression parameters are:

$$\begin{aligned} \frac{\partial LL}{\partial \beta_j} &= \sum_{i=1}^{n} \frac{\partial g}{\partial \eta_i} \frac{\partial \eta_i}{\partial \beta_j} \\ &= \sum_{i=1}^{n} x_{ij} \frac{\partial g}{\partial \eta_i} \qquad (4.2) \\ \frac{\partial^2 LL}{\partial \beta_j \beta_k} &= \sum x_{ij} x_{ik} \frac{\partial^2 g}{\partial \eta_i^2}\,, \qquad (4.3) \end{aligned}$$

where $\eta = X'\beta$ is the vector of linear predictors.

Ignore for a moment the derivatives with respect to σ (or treat it as fixed). The Newton-Raphson step defines an update δ

$$(X^T D X)\delta = X^T U,$$

where D is the diagonal matrix formed from $-g''$, and U is the vector g'. The current estimate β satisfies $X\beta = \eta$, so that the new estimate $\beta + \delta$ will have

$$\begin{aligned} (X^T D X)(\beta + \delta) &= X^T D\eta + X^T U \\ &= (X^T D)(\eta + D^{-1}U) \end{aligned}$$

Thus if we treat σ as fixed, iteration is equivalent to IRLS with weights of $-g''$ and adjusted dependent variable of $\eta - g'/g''$. At the solution to the iteration we might expect that $\hat{\eta} \approx y$; and a weighted regression with y replacing η gives, in general, good starting estimates for the iteration. (For an interval censored observation we use the center of the interval as 'y'). Note that if all of the observations are uncensored, then this reduces to using the linear regression of y on X as a starting estimate: $y = \eta$ so $z = 0$, thus $g' = 0$ and $g'' =$ a constant (all of the supported densities have a mode at zero).

This clever starting estimate is introduced in Generalized Linear Models (McCullagh and Nelder [7]), and works extremely well in that context: convergence often occurs in 3-4 iterations. It does not work quite so well here, since a "good" fit to a right censored observation might have $\eta >> y$. Secondly, the other coefficients are not independent of σ, and σ often appears to be the most touchy variable in the iteration.

Most often, the routines will be used with $\log(y)$, which corresponds to the set of accelerated failure time models. The transform can be applied implicitly or explicitly; the following two fits give identical coefficients:

```
> fit1 <- survreg(Surv(futime, fustat)~ age + rx, fleming, dist='weibull')
> fit2 <- survreg(Surv(log(futime), fustat) ~ age + rx, data=fleming,
                dist='extreme')
```

The log-likelihoods for the two fits differ by a constant, i.e., the sum of $d\log(y)/dy$ for the uncensored observations, and certain predicted values and residuals will be on the y versus $\log(y)$ scale.

4.8 Derivatives

This section is very similar to the appendix of Escobar and Meeker [1], differing only in our use of $\log(\sigma)$ rather than σ as the natural parameter. Let f and F denote the density and distribution functions, respectively, of the distributions. Using (4.1) as the definition of $g1, \ldots, g4$ we have

$$\begin{aligned}
\frac{\partial g_1}{\partial \eta} &= -\frac{1}{\sigma}\left[\frac{f'(z)}{f(z)}\right] \\
\frac{\partial g_4}{\partial \eta} &= -\frac{1}{\sigma}\left[\frac{f(z^u) - f(z^l)}{F(z^u) - F(z^l)}\right] \\
\frac{\partial^2 g_1}{\partial \eta^2} &= \frac{1}{\sigma^2}\left[\frac{f''(z)}{f(z)}\right] - (\partial g_1/\partial \eta)^2 \\
\frac{\partial^2 g_4}{\partial \eta^2} &= \frac{1}{\sigma^2}\left[\frac{f'(z^u) - f'(z^l)}{F(z^u) - F(z^l)}\right] - (\partial g_4/\partial \eta)^2 \\
\frac{\partial g_1}{\partial \log \sigma} &= -\left[\frac{z f'(z)}{f(z)}\right] \\
\frac{\partial g_4}{\partial \log \sigma} &= -\left[\frac{z^u f(z^u) - z^l f(z^l)}{F(z^u) - F(z^l)}\right] \\
\frac{\partial^2 g_1}{\partial (\log \sigma)^2} &= \left[\frac{z^2 f''(z) + z f'(z)}{f(z)}\right] - (\partial g_1/\partial \log \sigma)^2 \\
\frac{\partial^2 g_4}{\partial (\log \sigma)^2} &= \left[\frac{(z^u)^2 f'(z^u) - (z^l)^2 f'(z_l)}{F(z^u) - F(z^l)}\right] - \partial g_1/\partial \log \sigma (1 + \partial g_1/\partial \log \sigma) \\
\frac{\partial^2 g_1}{\partial \eta \partial \log \sigma} &= \frac{z f''(z)}{\sigma f(z)} - \partial g_1/\partial \eta (1 + \partial g_1/\partial \log \sigma) \\
\frac{\partial^2 g_4}{\partial \eta \partial \log \sigma} &= \frac{z^u f'(z^u) - z^l f'(z^l)}{\sigma [F(z^u) - F(z^l)]} - \partial g_4/\partial \eta (1 + \partial g_4/\partial \log \sigma)
\end{aligned}$$

To obtain the derivatives for g_2, set the upper endpoint z_u to ∞ in the equations for g_4. To obtain the equations for g_3, left censored data, set the lower endpoint to $-\infty$.

After much experimentation, a further decision was made to do the internal iteration in terms of $\log(\sigma)$. This avoids the boundary condition at zero, and also helped the iteration speed considerably for some test cases. The changes to the code were not too great. By the chain rule

$$\begin{aligned}
\frac{\partial LL}{\partial \log \sigma} &= \sigma \frac{\partial LL}{\partial \sigma} \\
\frac{\partial^2 LL}{\partial (\log \sigma)^2} &= \sigma^2 \frac{\partial^2 LL}{\partial \sigma^2} + \sigma \frac{\partial LL}{\partial \sigma} \\
\frac{\partial^2 LL}{\partial \eta \partial \log \sigma} &= \sigma \frac{\partial^2}{\partial \eta \partial \sigma}
\end{aligned}$$

At the solution $\partial LL/\partial \sigma = 0$, so the variance matrix for σ is a simple scale change of the returned matrix for $\log(\sigma)$.

4.9 Distributions

4.9.1 Gaussian

Everyone's favorite distribution. The continual calls to Φ may make it slow on censored data, however. Because there is no closed form for Φ, only the equations for g_1 simplify from the general form given in section 2 above.

$$\begin{aligned} \mu = 0 \quad &, \quad \sigma^2 = 1 \\ F(z) &= \Phi(z) \\ f(z) &= \exp(-z^2/2)/\sqrt{2\pi} \\ f'(z) &= -zf(z) \\ f''(z) &= (z^2 - 1)f(z) \end{aligned}$$

For uncensored data, the standard glm results are clear by substituting $g_1 = -z/\sigma$ into equations 1-5. The first derivative vector is equal to $X'r$ where $r = -z/\sigma$ is a scaled residual, the update step $I^{-1}U$ is independent of the estimate of σ, and the maximum likelihood estimate of $n\sigma^2$ is the sum of squared residuals. None of these hold so neatly for right censored data.

4.9.2 Extreme value

If y is Weibull then $\log(y)$ is distributed according to the (least) extreme value distribution. As stated above, fits on the latter scale are numerically preferable because it removes the range restriction on y. A Weibull distribution with the scale restricted to 1 gives an exponential model.

$$\mu = -\gamma = .5722\ldots, \ \sigma^2 = \pi^2/6$$

$$\begin{aligned} F(z) &= 1 - \exp(-w) \\ f(z) &= we^{-w} \\ f'(z) &= (1 - w)f(z) \\ f''(z) &= (w^2 - 3w + 1)f(z) \end{aligned}$$

where $w \equiv exp(z)$.

The mode of the distribution is at $f(0) = 1/e$, so for an exact observation the deviance term has $\hat{y} = y$. For interval censored data where the interval is of length $b = z^u - z^l$, it turns out that we cover the most mass if the interval has a lower endpoint of $a = \log(b/(\exp(b) - 1)))$, and the resulting log-likelihood is

$$\log(e^{-e^a} - e^{-e^{a+b}}).$$

Proving this is left as an exercise for the reader.

The cumulative hazard for the Weibull is usually written as $\Lambda(t) = (at)^p$. Comparing this to the extreme value we see that $p = 1/\sigma$ and $a = \exp(-\eta)$. (On the hazard scale the change of variable from t to $\log(t)$ adds another term). The Weibull can be thought of as both an accelerated failure time model, with acceleration factor a or as a proportional hazards model with constant of proportionality a^p. If a Weibull model holds, the coefficients of a Cox model

will be approximately equal to $-\beta/\sigma$, the latter coming from a `survreg` fit. The change in sign reflects a change in perspective: in a proportional hazards model a positive coefficient corresponds to an increase in the death rate (bad), whereas in an accelerated failure time model a positive coefficient corresponds to an increase in lifetime (good).

4.9.3 Logistic

This distribution is very close to the Gaussian except in the extreme tails, but it is easier to compute. However, some data sets may contain survival times close to zero, leading to differences in fit between the lognormal and log-logistic choices. (In such cases the rationality of a Gaussian fit may also be in question). Again let $w = \exp(z)$.

$$\mu = 0,\ \sigma^2 = \pi^2/3$$

$$\begin{aligned} F(z) &= w/(1+w) \\ f(z) &= w/(1+w)^2 \\ f'(z) &= f(z)\,(1-w)/(1+w) \\ f''(z) &= f(z)\,(w^2 - 4w + 1)/(1+w)^2 \end{aligned}$$

The distribution is symmetric about 0, so for an exact observation the contribution to the deviance term is $-\log(4)$. For an interval censored observation with span $2b$ the contribution is

$$\log\left(F(b) - F(-b)\right) = \log\left(\frac{e^b - 1}{e^b + 1}\right).$$

4.9.4 Other distributions

Some other population hazards can be fit into this location-scale framework, some can not.

Distribution	Hazard
Weibull	$p\lambda(\lambda t)^{p-1}$
Extreme value	$(1/\sigma)e^{(t-\eta)/\sigma}$
Rayleigh	$a + bt$
Gompertz	bc^t
Makeham	$a + bc^t$

The Makeham hazard seems to fit human mortality experience beyond infancy quite well, where a is a constant mortality which is independent of the health of the subject (accidents, homicide, etc) and the second term models the Gompertz assumption that "the average exhaustion of a man's power to avoid death is such that at the end of equal infinitely small itervals of time he has lost equal portions of his remaining power to oppose destruction which he had at the commencement of these intervals". For older ages a is a neglible portion of the death rate and the Gompertz model holds.

Clearly

- The Wiebull distribution with $p = 2$ ($\sigma = .5$) is the same as a Rayleigh distribution with $a = 0$. It is not, however, the most general form of a Rayleigh.

- The extreme value and Gompertz distributions have the same hazard function, with $\sigma = 1/\log(c)$, and $\exp(-\eta/\sigma) = b$.

It would appear that the Gompertz can be fit with an identity link function combined with the extreme value distribution. However, this ignores a boundary restriction. If $f(x;\eta,\sigma)$ is the extreme value distribution with paramters η and σ, then the definition of the Gompertz densitiy is

$$\begin{aligned} g(x;\eta,\sigma) &= 0 & x < 0 \\ g(x;\eta,\sigma) &= cf(x;\eta,\sigma) & x >= 0 \end{aligned}$$

where $c = \exp(\exp(-\eta/\sigma))$ is the necessary constant so that g integrates to 1. If η/σ is far from 1, then the correction term will be minimal and the above fit will be a good approximation to the Gompertz.

The Makeham distribution falls into the gamma family (equation 2.3 of Kalbfleisch and Prentice, Survival Analysis), but with the same range restriction problem.

Chapter 5

Tied event times

5.1 Cox model estimates

The theory for the Cox model has always been worked out for the case of continuous time, which implies that there will be no tied event or censoring times in the data set. With respect to censoring times, all of the survival library commands treat censoring as occuring "just after" the recorded time point. The rationale is that if a subject was last observed alive on day 231, say, then their death time, whatever it is, must be strictly greater than 231. For formally, a subject who was censored at time t is considered to have been at risk for any events that occured at time t.

The issue with tied event times is more complex, and the software supports three different algorithms for dealing with this. The Cox partial likelihood is a sum of terms, one for each event time, each of which compares the subject who had the event to the set of subjects who "could have had the event": the *risk set*. The overall view is essentially a lottery model: at each event time there was a drawing to select one subject for the event, the risk score for each subject $\exp(X_i\beta)$ tells how many "tickets" each subject had in the drawing. The software implements three different algorithms for dealing with tie event times.

The Breslow approximation (`ties='breslow'`) in essence ignores the ties. If two subjects A and B died on day 100, say, the partial likelihood will have separate terms for the two deaths. Subject A will be at risk for the death that happened to B, and B will be at risk for the death that happened to A. In life this is not technically possible of course: whoever died first will not be at risk for the second death.

The Efron approximation can be motivated by the idea of *coarsening*: time is on a continuous scale but we only observe a less precise version of it. For example consider the acute myelogenous leukemia data set that is part of the package, which was a clinical trial to test if extendend chemotherapy ("Maintained") was superior to standard. The time to failure was recorded in months, and in the non-maintained arm there are two pairs of failures, at 5 and at 8 months. It might be reasonable to assume that if the data had been recored in days these ties might not have occured.

```
> with(subset(aml, x=="Nonmaintained"), Surv(time, status))
 [1]  5   5   8   8  12  16+ 23  27  30  33  43  45
```

Let the risk scores $\exp(X\beta)$ for the 12 subjects be r_1–r_{12}, and assume that the two failures actually at month 5 are not tied on a finer time scale. For the first event, whichever it is, the risk set with be all subjects 1–12 and the denominator of the partial likelihood term is $\sum r_i$. For the second event, the denominator is either $r_1+r_3+\ldots r_{12}$ or $r_2+r_3+\ldots r_{12}$; the Efron approximation is to use the average of the two as the denominator term. In the software this is easily done by using temporary case weights: if there were k tied events then one of the denomiators gives each of those k subjects a weight of 1, then next gives each a weight of $(k-1)/k$, then next a weight of $(k-2)/k$, etc. The Efron approximation imposes a tiny bit more bookkeeping, but the the computational burden is no different that for case weights; i.e., it effectively takes no more computational time than the Breslow approximation.

The third possiblility is the exact partial likelihood due to Cox, which treats the underlying time scale as discrete rather than continuous. When taking this view the denominator of the partial likelihood term is again an average, but over a much larger subset. If there are k events and n subjects at risk, the EPL sum is over all k choose n possible choices. In the AML example above, the event at time 5 will be a sum over $12(11)/2 = 33$ terms. If the number of ties is large this quickly grows unreasonable: for 20 ties out of 1000 the sum has over 39 billion terms. A clever algorithm by Gail makes this sum barely possible, but it does not extend to the case of (tstart, tstop) style data.

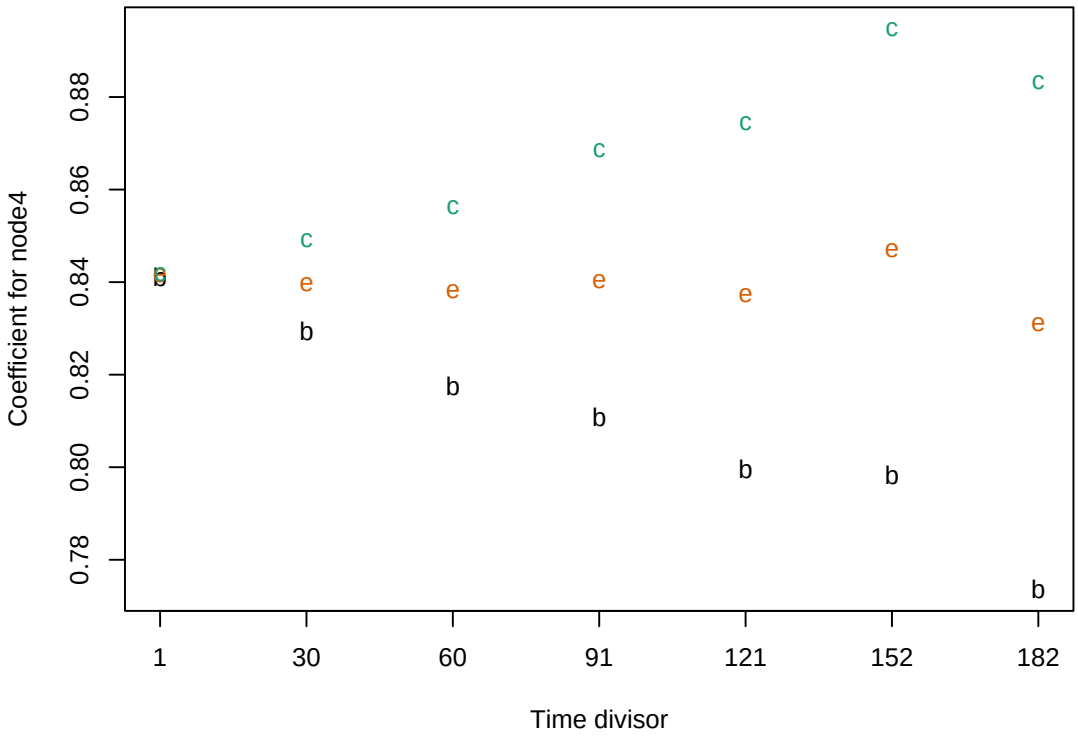
An important aside is that the log-likelihood for matched logistic regression is identical to the Cox partial likelihood for a particular data set, when the EPL is used. Namely, set time=1 (or any other constant), status = 0 for controls and 1 for cases, and fit a coxph model with each matched set as a separate stratum. In most instances a matched set will consist of a single case along with one or more controls, however, which is the case where the Breslow, Efron, and EPL are identical. (The EPL will still take slightly longer to run due to setting up the necessary structure for all those sums.)

How important are the ties, actually? Below we show a small computation in which a larger data set is successively coarsened and compare the results. The colon cancer data set has 929 subjects with stage B/C colon cancer who were randomized to three treatment arms and then followed for 5 years; the time to death or progression is in days. In the example below we successively coarsen the time scale to be monthly, bimonthly, ..., bi-annual; the last of which generates an very large number of ties. What we see is that

- The Efron approximation is quite good at dealing with the coarsened data, producing nearly the same coefficient as the original data even when the coarsening is extreme.
- The Breslow approximation is biased somewhat towards 0, the exact paritial likelihood somewhat away from 0.
- The differences are very small. With monthly coarsening, which is itself fairly large, the 3 estimates differ by about .01 while the standard error of the original coefficient is 0.96; i.e. a shift that is statistically immaterial.

```
> tdata <- subset(colon, etype==1)   # progression or death
> cmat <- matrix(0, 7, 6)
> for( i in 1:7) {
      if (i==1) scale <-1 else scale <- (i-1)*365/12
```

```
        temp <- floor(tdata$time/scale)
        tfit <-  coxph(Surv(temp, status) ~ node4 + extent, tdata)
        tfit2 <- coxph(Surv(temp, status) ~ node4 + extent, tdata,
                       ties='breslow')
        tfit3 <- coxph(Surv(temp, status) ~ node4 + extent, tdata,
                       ties='exact')
        cmat[i,] <- c(coef(tfit2), coef(tfit), coef(tfit3))
    }
> matplot(1:7, cmat[,c(1,3,5)], xaxt='n', pch='bec',
            xlab="Time divisor", ylab="Coefficient for node4")
> axis(1, 1:7, c(1, floor(1:6 *365/12)))
```



Early on in the package the decision was made to make the Efron approximation the default. The reasoning was simply that is *is* more accurate, even if only a little, and the author's early background in numerical analysis argued strongly to always use the best approximation available. The second reason is that the computational cost is low. Most of us would pick up a 1 Euro coin on the sidewalk, even though it will not make any real change in our income. One downside is that no other package did this, leading to a very common complaint/question that R "gives different results". A second is that it leads to further downstream programming as discussed in following sections.

5.2 Cumulative hazard and survival

The coarsening argument can also be applied to the cumulative hazard $\Lambda(t)$. Say that there were 3 deaths with 10 subjects at risk. The increment to the Nelson-Aalen cumulative hazard estimate would then be 3/10. If the data had been observed in continuous time, however, there would have been 3 increments of $1/10 + 1/9 + 1/8$. This estimate was explored by Fleming and Harrington [2]. In the `survfit` function the `ctype` option selects for 1=Nelson-Aalen and 2= Fleming-Harrington.

The Kaplan-Meier estimate is not subject to the coarsening phenominon. In our example, the observed data will lead to a multipilicative increment of 7/10 and the continuous data to one of $(9/10)(8/9)(7/8)$, which are the same. An alternate estimate of the survival is $S(t) = \exp(-\Lambda(t))$. Basing this on the FH estimate of hazard will more closely track the KM when there are tied event times. The direct (KM) vs. exponential estimates of survival are obtained with the `ctype=1` and `ctype=2` arguments; however, the exponential estimate is quite uncommon outside of the Cox model.

5.3 Predicted cumulative hazard and survival from a Cox model

Predictions from a coxph model must always be for *someone*, i.e., some particular set of covariate values. Let $r_i = \exp(X_i\hat{\beta} - c)$ be the recentered risk scores for each subject i, where the recentering constant $c = X_n\hat{\beta}$, X_n being the covariates of the "new" subject for which prediction is desired. (We don't want to create a prediction for a baseline subject with X=0, what textbooks often call a "baseline hazard", since if 0 is too far from the center of the data the exp function can easily overflow.) The estimated cumulative hazard at any event time is then

$$\hat{\Lambda}(t) = \int_0^t \frac{\sum_i dN_i(t)}{\sum_i Y_i(t) r_i} \tag{5.1}$$

Equation (5.1) is known as the Breslow estimate; if $\hat{\beta} = 0$ then $r_i = 1$ and it becomes equal to the Nelson-Aalen estimator.

If the Efron estimate is used for ties, then the software uses an Efron estimate of the cumulative hazard; which reduces to the Fleming-Harrington if $\hat{\beta} = 0$. Using the hazard estimate that matches the parial likelihood estimate causes an important property of the vector of martingale residuals m to hold, namely that mX is equal to the first derivative of the partial likelihood. residuals hold for both

The Cox model is a case where the default estimate of survival is based on the exponent of the cumulative hazard, rather than a 'direct' one such as the Kaplan-Meier. There are three reasons for this.

1. The most obvious 'direct' estimate is to use $(\sum dN_i(t) - \sum Y_i(t) r_i)/(\sum Y_i(t) r_i)$ as a multiplicative update at each event time t. This expression in not guarranteed to be between 0 and 1, however, particular for new subjects who are near or past the boundaries of the original data set. This leads to using some sort of ad hoc correction to avoid failure.

2. The direct estimate of Kalbfleisch and Prentice avoids this, but it does not extend to delayed entry, multi-state models or other extensions of the basic model.

3. The KP estimate reqires iteration so the code is more complex.

Chapter 6

Multi-state models

Multi-state hazards models have a very interesting (and useful) property, which is that hazards can be estimated singly (without reference to any other transition) but probability-in-state estimators must be computed globally. Thus, one can estimate non-parametric cumulative hazard estimates (Nelson-Aalen), the hazard ratios for any given transtion (Cox model) or the predicted cumulative hazard function based on a per transition Cox model without incurring any issues with respect to competing risks. (If there is informative censoring the overall and individual estimates still agree, but they will both be wrong. An example of informative censoring would be subjects who are removed from the data because of an impending event, e.g., censoring subjects who enter hospice care would underestimate death rates.)

Now say that we had a simple competing risks problem, 10 subjects are alive and in the initial state on day 100, at which time two of them transition to two different endpoints. A coarsening argument would say that on the underlying continuous time scale these two subjects would not be tied, and then would use 9.5 as the denominator for each of the two cumulative hazard increments. Such an estimate would however then be at variance with the two indiviually computed hazards: global coarsening removes the separability. The survival package takes a moderated view and will apply the coarsening argument separately to each hazard, i.e., it chose to retain the separation policy.

Appendix A

Changes from version 2.44 to 3.1

A.1 Changes in version 3

Some common concepts had appeared piecemeal in more than one function, but not using the same keywords. Two particular areas are survival curves and multiple observations per subject.

Survival and cumulative hazard curves are generated by the `survfit` function, either from raw data (survfit.formula), or a fitted Cox or parametric survival model (survfit.coxph, survfit.survreg). Two choices that appear are:

1. If there are tied event times, to estimate the hazard using a straightforward increment of (number of events)/(number at risk), or make a correction for the ties. The simpler method is known variously as the Nelson, Aalen, Breslow, and Tsiatis estimate, along with hyphenated forms combining 2 or 3 of these labels. One of the simpler corrections for ties is known as the Fleming-Harrington approximation when used with raw data, and the Efron when used in a Cox model.

2. The survival curve $S(t)$ can be estimated directly or as the exponential of the cumulative hazard estimate. The first of these is known as the Kaplan-Meier, cumulative incidence (CI), Aalen-Johansen, and Kalbfleisch-Prentice estimate, depending on context, the second as a Fleming-Harrington, Breslow, or Efron estimate, again depending on context.

With respect to the two above, subtypes of the `survfit` routine have had either a `type` or `method` argument over the years which tried to capture both of these at the same time, and consequently have had a bewildering number of options, for example "fleming-harrington" in `survfit.formula` stood for the simple cumulative hazard estimate plus the exponential survival estimate, "fh2" specified the tie-corrected cumulative hazard plus exponential survival, while `survfit.coxph` used "breslow" and "efron" for the same two combinations. The updated routines now have separate `stype` and `ctype` arguments. For the first, 1= direct and 2=exponent of the cumulative hazard and for the second, 1=simple and 2= corrected for ties.

The Cox model is a special case in two ways: 1. the the way in which ties are treated in the likelihood should match the way they are treated in creating the hazard and 2. the direct estimate of survival can be very difficult to compute. The survival package's default is to use the

`ctype` option which matches the ties option of the `coxph` call along with an exponential estimate of survival. This `ctype` choice preserves some useful properties of the martingale residuals.

A second issue is multiple observations per subject, and how those impact the computations. This leads to 3 common arguments:

- id: an identifier in each row of the data, which allows the routines to identify multiple rows for a subject
- cluster: identify correlated rows, which should be combined when creating the robust variance
- robust: TRUE or FALSE, to compute a robust variance.

These arguments have been inconsistent in the past, partly because of the sequential appearance of multiple use cases. The package started with only the simplest data form: one observation per subject, one endpoint. To this has been added:

a. Multiple observations per subject

b. Multiple endpoints per subject

c. Multiple types of endpoints

Case (a) arises as a way to code time-dependent covariates, and in this case an `id` statement is not needed, and in fact you will get the same estimates and standard errors with or without it. (There will be a change in the counts of subjects who leave or enter an interval, since an observation pair (0, 10), (10, 20) for the same subject will not count as an exit (censor) at 10 along with an entry at 10.) If (b) is true then the robust variance is called for and one will want to have either a `cluster` argument or the `robust=TRUE` argument. In the coxph routine, a `cluster(group)` term in the model statement can be used instead of the cluster argument, but this is no longer the preferred form. When (b) and (c) are true then the `id` statement is required in order to obtain a correct *estimate* of the result. This is also the case for (c) alone when subjects do not all start in the same state. For competing risks data — multiple endpoints, everyone starts in the same state, only one transition per subject — the `id` statement is not necessary nor (I think) is a robust variance.

When there is an `id` statement but no `cluster` or `robust` directive, then the programs will use (b) as a litmus test to decide between model based or robust variance, if possible. (There are edge cases where only one of the two variance estimates has been implemented, however). If there is a `cluster` argument then `robust=TRUE` is assumed. If only a `robust=TRUE` argument is given then the code treats each line of data as independent.

A.2 Survfit

There has been a serious effort to harmonize the various survfit methods. Not all paths had the same options or produced the same outputs.

- Common arguments of id, cluster, influence, stype and ctype.

  - If stype=1 then the survival curve S(t) is produced directly, if stype=2 it is created as the exp(-H) where H is the cumulative hazard.
  - If ctype=1 the Nelson-Aalen formula is used, and for ctype=2 there is a correction for ties.
  - The usual curve for a Cox model using the Efron approximate is (2,2), for instance, while the ordinary non-parametric KM is (1, 1).

- The routines now produce both the estimated survival and the estimated cumulative hazard, along with their errors
- Some code paths produce std(S) and some std(log(S)), the object now contains a `log.se` flag telling which. (Before, downstream routines just "had to know").
- using a single subscript on a survfit object now behaves like the use of a single subscript on an array or matrix, in that the result has only one dimension.

A utility function `survfit0` is used by the print and plot methods to add a starting "time 0" value, normally x=0, y=1, to the survival curve(s). It also aligns all the matrices so that they correspond to the time vector, inserts the correct standard errors, etc. This may be useful to other programs.

A.3 Coxph

The multi-state objects include a `states` vector, which is a simple list of the state names. The `cmap` component is an integer matrix with one row for each term in the model and one column for each transition. Each element indexes a position in the coefficient vector and variance matrix.

- Column labels are of the form 1:2, which denotes a transition from `state[1]` to `state[2]`.
- If a particular term in the data, "age" say, was not part of the model for a particular transition then a 0 will appear in that position of `cmap`.
- If two transitions share a common coefficient, both those element of `cmap` will point to the same location.
- Following the coefficient information will be a row labeled `(Baseline)`, which contains integers identifing which transitions do or do not share their baseline hazard.
- Following this are rows for each strata term (if any) in the model, each a 0/1 vector which marks transitions to which this strata applies.

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