Chapter 11

Survival Data and the Kaplan-Meier Curve

We have already investigated supervised learning models and hypothesis tests in cases where the outcome of interest is a category or number. But what if the outcome is a *time duration*? For example, what if we're comparing the effects of two treatments and our outcome is the time between treatment administration and disease progression?

Data where the outcome is a time duration are very common in clinical data science and are called **time-to-event** data or **survival data**. The field of **survival analysis** develops methods to analyze and interpret such data. We will examine one such method today and many more in subsequent chapters.

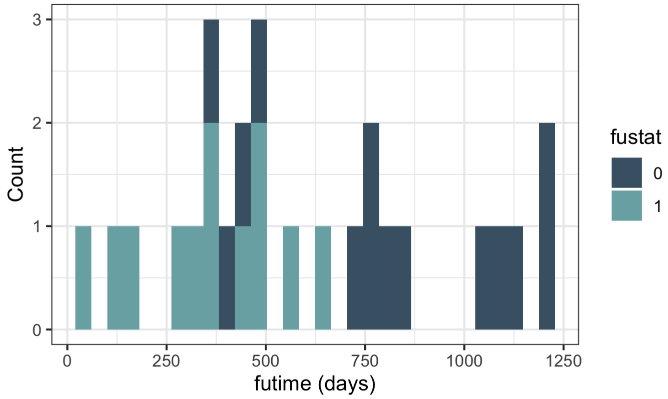
11.1 Example: Ovarian Cancer Survival Dataset

Today we'll examine some data from a study of ovarian cancer[1]. The dataset contains information on 26 women. The variables are:

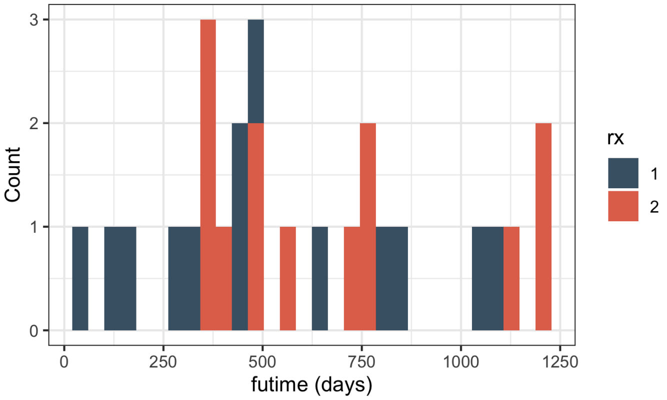
[1] The dataset comes from the `survival` package in R and is labeled `ovarian`. The original study is Edmonson JH *et al*, "Different chemotherapeutic sensitivities and host factors affecting prognosis in advanced ovarian carcinoma versus minimal residual disease", *Cancer Treatment Reports*, 63(2): 241-247; 1979.

- `futime`: The number of days from enrollment in the study until death or censoring, whichever came first
- `fustat`: An indicator of death (1) or censoring (0)
- `age`: The patient's age in years at the time of treatment administration
- `resid.ds`: Residual disease present at the time of treatment administration (1 = no, 2 = yes)
- `rx`: Treatment group (1 = cyclophosphamide, 2 = cyclophosphamide + adriamycin)
- `ecog.ps`: A measure of performance score or functional status at the time of treatment administration, using the Eastern Cooperative Oncology Group's (ECOG) scale. It ranges from 0 (fully functional) to 4 (completely disabled). Level 4 subjects are usually considered too ill to enter a randomized trial such as this. The patients in this dataset are all at Levels 1 and 2.

Here is a histogram of the follow-up times (`futime`) in days, colored according to whether the patient died or was censored (`fustat`):



And here is the same graph colored by treatment group (`rx`):



Now, imagine that we want to study the effect of the treatment group (`rx`) on the outcome of death or no death (1 = death, 0 = no death). We could think of this as a classification problem with only a single feature: treatment group. Unfortunately, this method of analyzing time-dependent data is fraught with problems:

1. How do you choose the time horizon at which to evaluate mortality?
2. How do you handle people who dropped out of the study before that time?

11.2 Definitions

Censoring occurs when the event of interest in a time-to-event analysis is not observed. It is a form of missing data problem (see Chapter **??**) and can be caused by a variety of factors, including inconsistencies in follow-up, the study's ending before all subjects have experienced the event, or a lack of knowledge about when, exactly, the event occurred. The type of censoring represented in the `ovarian` dataset is called **right-censoring**. We will focus on right-censoring today and investigate other types later.

> **Right censoring:** A situation that arises when the event of interest has not occurred by the end of the follow-up period. This may be because (a) the study itself ends, (b) a patient is lost to follow-up

during the study period, or (c) a patient experiences a different event that makes further follow-up impossible[2].

Survival data are generally described using two probabilities, called the survival and hazard.

Survival: Also called the **survival function** or **survival probability** and abbreviated $S(t)$, this is the probability that an individual survives to time t (i.e., does not experience the event by time t).

Hazard: Usually denoted by $h(t)$ or $\lambda(t)$, this is the probability that an individual who has not yet experienced the event at time t experiences it at that exact time. In other words, it is the instantaneous event rate for an individual who has already survived to time t.

We will focus on the survival function now and learn more about the hazard later.

11.3 The Kaplan-Meier Estimator

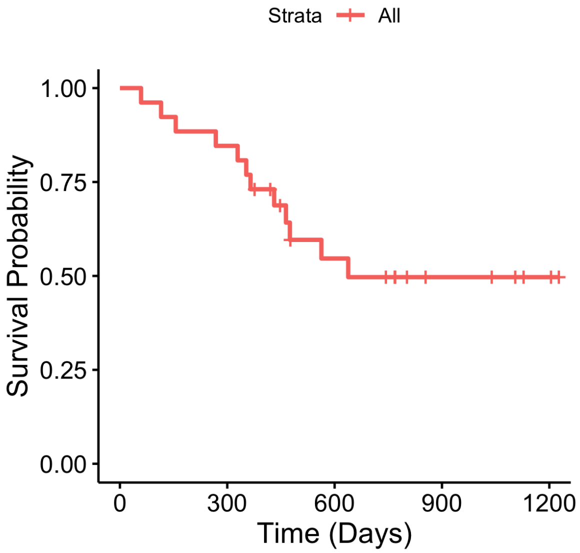
The **Kaplan-Meier estimator** is a nonparametric estimate of the survival function, usually represented graphically by a **Kaplan-Meier curve**[3]. The Kaplan-Meier estimator looks like this:

$$\hat{S}(t) = \prod_{j|t_j \leq t} \frac{n_j - d_j}{n_j}$$

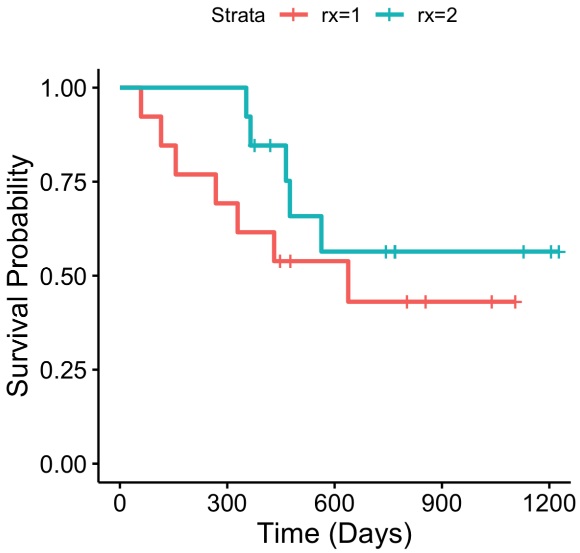
where d_j is the number of subjects who fail at time t_j and n_j is the number of subjects at risk just prior to t_j. Here is a Kaplan-Meier curve for the `ovarian` dataset. The little "+" signs correspond to censoring events.

[2] For more information, please see Clark TG *et al*, "Survival Analysis Part I: Basic Concepts and First Analyses", *British Journal of Cancer*, 89, 232–238; 2003.

[3] It can be shown mathematically that the Kaplan-Meier estimator is the maximum likelihood estimator (see Chapter 5) of the survival function in the case of censoring.



And here are Kaplan-Meier curves for the two treatment groups separately:



Question 11.1

Here are the raw data from treatment group 1 of the `ovarian` dataset. Using these data, fill in the remaining cells of the table below.

	rx	futime	fustat
1	1	59	1
2	1	115	1
3	1	156	1
4	1	268	1
5	1	329	1
6	1	431	1
7	1	448	0
8	1	477	0
9	1	638	1
10	1	803	0
11	1	855	0
12	1	1040	0
13	1	1106	0

j	t_j	n_j	d_j	$\hat{S}(t_j)$	Calculation
0	0	13	0	1.000	$\frac{13-0}{13}$
1	59	13	1	0.923	$\hat{S}(t_0)\left(\frac{13-1}{13}\right)$
2	115	12	1	0.846	$\hat{S}(t_1)\left(\frac{12-1}{12}\right)$
3	156				
4	268				
5	329	9	1	0.615	$\hat{S}(t_4)\left(\frac{9-1}{9}\right)$
6	431	8	1	0.538	$\hat{S}(t_5)\left(\frac{8-1}{8}\right)$
7	448	7	0	0.538	$\hat{S}(t_6)\left(\frac{7-0}{7}\right)$
8	477	6	0	0.538	$\hat{S}(t_7)\left(\frac{6-0}{6}\right)$
9	638	5	1	0.431	$\hat{S}(t_8)\left(\frac{5-1}{5}\right)$
10	803	4	0		
11	855	3	0		
12	1040	2	0		
13	1106	1	0		

Question 11.2

Based solely on the Kaplan-Meier curves for the two treatment groups, which treatment appears to prolong survival more effectively?

11.4 Assumptions of the Kaplan-Meier Estimator

The Kaplan-Meier estimator makes three important assumptions:

1. The probability of censoring is unrelated to the outcome of interest.
2. The survival probabilities are the same for participants recruited at different times during the study (e.g., circumstances that could alter the survival, such as treatments, do not change over calendar time).
3. The events occurred at exactly the times specified.

Question 11.3

What is one way each of these assumptions could be violated?

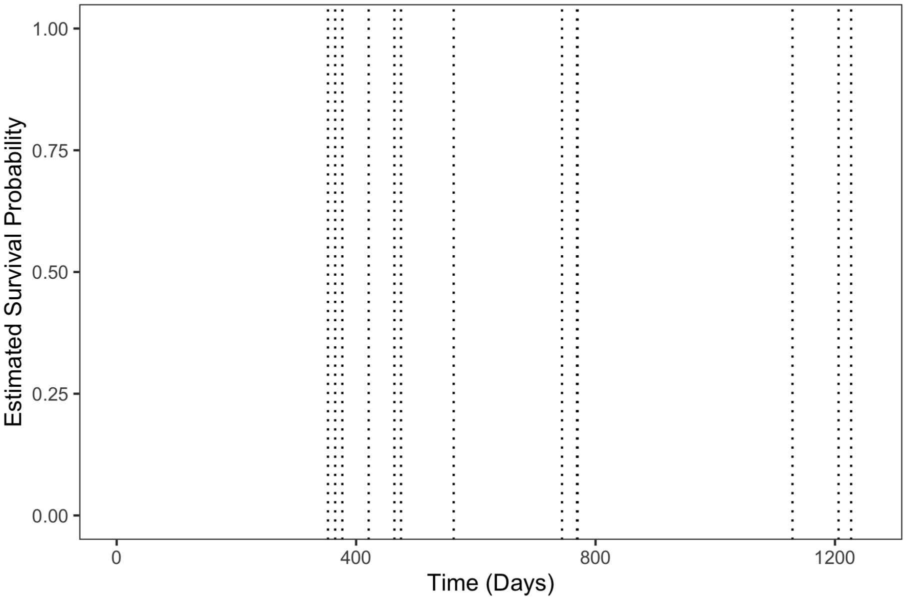
11.5 Comparing Kaplan-Meier Curves

Of course, now the question arises: How do we formally compare two Kaplan-Meier curves? There is a nonparametric hypothesis test for comparing Kaplan-Meier curves called the log-rank test; we will see it in Chapter **??**. There is also an entire family of linear models, called Cox proportional hazards models, that use the Kaplan-Meier curve as their backbone and model the effects of different covariates on this curve. We will see them in Chapter 18.

Question 11.4

Here are the data for treatment group 2 of the `ovarian` dataset. Perform the calculations of $\hat{S}(t_j)$ for $j = 0, \ldots, 13$, starting with $t_0 = 0$. Draw the Kaplan-Meier curve, adding symbols for the censoring events.

	rx	futime	fustat
1	2	353	1
2	2	365	1
3	2	377	0
4	2	421	0
5	2	464	1
6	2	475	1
7	2	563	1
8	2	744	0
9	2	769	0
10	2	770	0
11	2	1129	0
12	2	1206	0
13	2	1227	0



Chapter 18

The Cox Proportional Hazards Model

We just encountered the Kaplan-Meier estimate of the survival function in Chapter 11. Now we are going to talk about models that essentially treat the survival function as the *outcome* in a supervised learning problem. These models are called **Cox proportional hazards models**.

18.1 Survival and Hazard Functions

Consider a situation where we have some process that generates events, and we're trying to model the time to first event. Assume the probability of the event's occurring at each time, t, is given by the function $f(t)$. The cumulative probability of the event's having occurred by time t is

$$F(t) = \int_0^t f(t)dt$$

and the probability of an individual not having experienced the event by time t is

$$S(t) = 1 - F(t),$$

the **survival function**. The probability of experiencing the event in an infinitesimally small interval starting at t, given that one has not experienced it by time t, is:

$$\lambda(t) = \frac{f(t)}{S(t)}$$

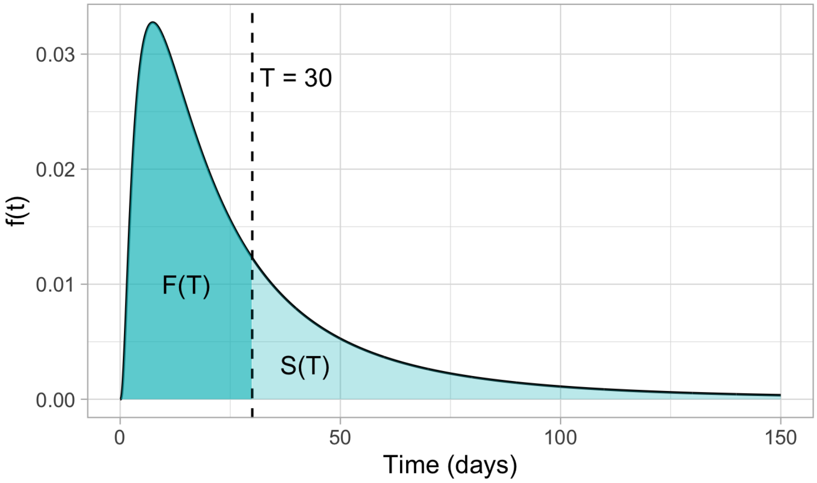
and is called the **hazard**. The **cumulative hazard** function is equal to

$$\Lambda(t) = \int_0^t \lambda(t')dt' = -\log S(t)$$

so $S(t) = \exp(-\Lambda(t))$.

None of these expressions should be immediately obvious to you, because deriving them requires calculus. It's a great exercise to go through the derivations, but for now, let's focus on capturing the intuition.

Here is a graphical representation of some of these quantities. Remember that the probability distribution $f(t)$ must integrate to one.



Question 18.1

What's the interpretation of the hazard, $\lambda(t)$, on this image? What happens to the hazard if $S(t)$ is low vs. high for the same $f(x)$?

Question 18.2

Assume $f(t)$ is exponential: $f(t) = b \cdot \exp(-bt)$, where b is constant. Then $F(t) = 1 - \exp(-bt)$ and $S(t) = \exp(-bt)$. What is the hazard, $\lambda(t)$? What is the cumulative hazard, $\Lambda(t)$?

Question 18.3

The concept of a "cumulative hazard" is pretty weird. How should this quantity be interpreted?

18.2 Estimating Survival and Cumulative Hazard

The Kaplan-Meier estimate of survival (Chapter 11) is the most common estimate of the survival function. One can estimate the cumulative hazard using a couple of different methods.

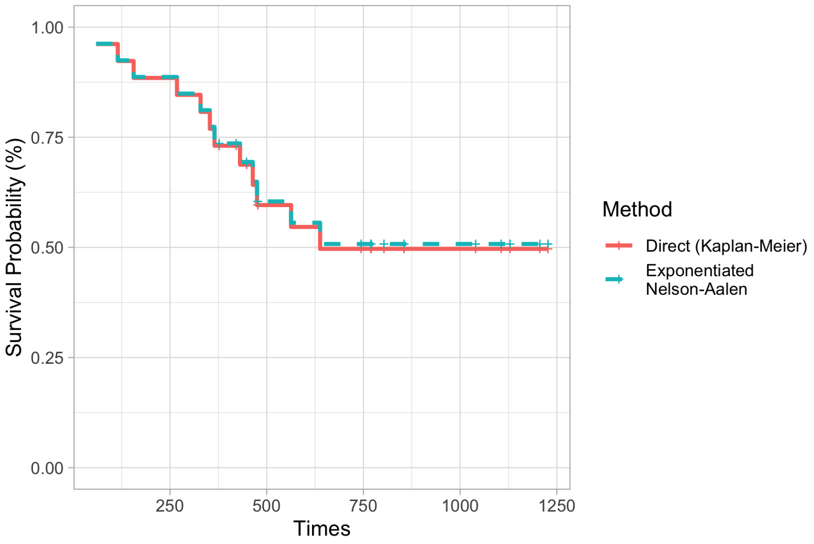
1. Take the negative log of the Kaplan-Meier estimate of survival:

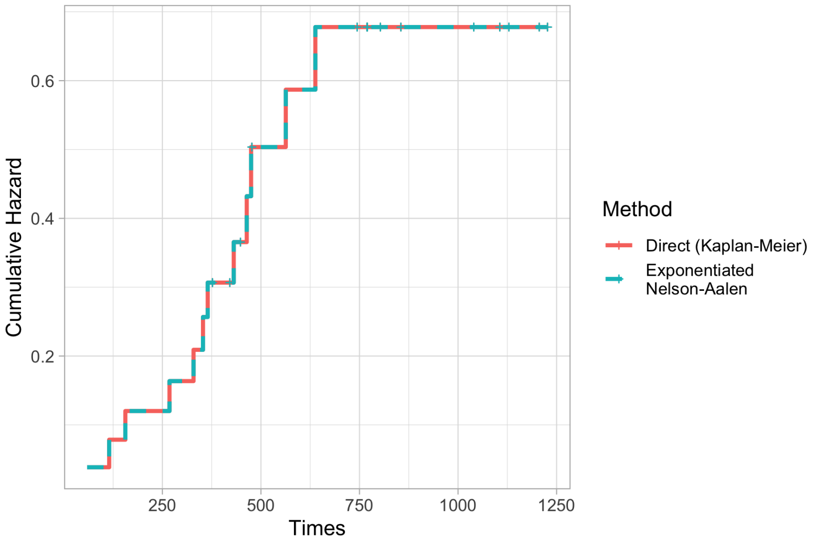
$$\begin{aligned}\hat{\Lambda}_{KM}(t) &= -\log \hat{S}_{\text{KM}}(t) \\ &= -\sum_{i:t_i<t} \log\left(1 - \frac{d_i}{n_i}\right)\end{aligned}$$

2. Use the **Nelson-Aalen estimator**

$$\hat{\Lambda}_{NA}(t) = \sum_{i:t_i<t} \frac{d_i}{n_i}$$

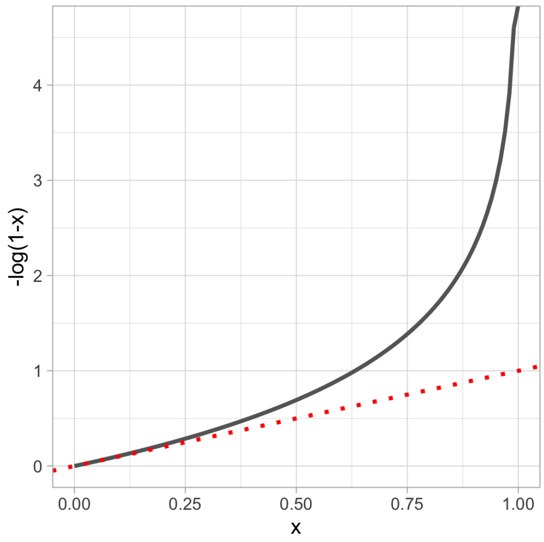
One thing that is confusing about the R `survival` package's output is that is uses the Kaplan-Meier estimate for survival by default, but it uses the Nelson-Aalen estimator for cumulative hazard by default. So if you exponentiate the negative cumulative hazard that comes out of `survfit`, it won't match the survival estimate. The two are close in most cases, though. Here are some pictures for the ovarian cancer survival dataset we discussed in Chapter 11:


1.00
0.75
0.50
0.25
0.00
Survival Probability (%)
250
500
750
1000
1250
Times
Method
Direct (Kaplan-Meier)
Exponentiated
Nelson-Aalen


0.6
0.4
0.2
Cumulative Hazard
250
500
750
1000
1250
Times
Method
Direct (Kaplan-Meier)
Exponentiated
Nelson-Aalen

Question 18.4

Here is a plot showing the function $-\log(1-x)$ vs. x. Look at the expressions for the two estimators for the cumulative hazard, above. Under what conditions will they be similar? Under what conditions will they be different?



Question 18.5

The curvature of the Nelson-Aalen estimator gives you an idea of how the hazard varies with time. A concave shape is an indication of *deceleration* of the hazard; for example, if the event in question is death and time is patient age, this would represent higher infant/childhood mortality than adult mortality. A convex shape is an indication of *acceleration* of the hazard; in the death/age example, this would represent a process that accelerates as one ages (so called "wear-out mortality").

Looking at the graph of the overall cumulative hazard, what do you notice about how the hazard for ovarian cancer changes since the initiation of treatment?

Question 18.6

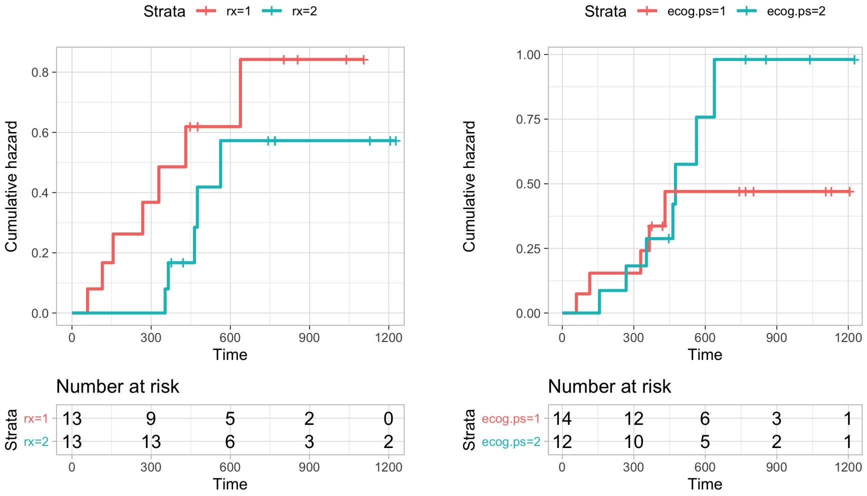
Here are the raw data from treatment group 1 of the `ovarian` dataset. These are the same data we looked at when building the Kaplan-Meier curve in Chapter 11, Question 11.1. Using these data, fill in the remaining cells of the table below. Here we are using the Nelson-Aalen estimator for the cumulative hazard.

	rx	futime	fustat
1	1	59	1
2	1	115	1
3	1	156	1
4	1	268	1
5	1	329	1
6	1	431	1
7	1	448	0
8	1	477	0
9	1	638	1
10	1	803	0
11	1	855	0
12	1	1040	0
13	1	1106	0

j	t_j	n_j	d_j	$\hat{\Lambda}(t_j)$	Calculation
0	0	13	0	0.000	$\frac{0}{13}$
1	59	13	1	0.077	$\hat{\Lambda}(t_0) + \frac{1}{13}$
2	115	12	1	0.160	$\hat{\Lambda}(t_1) + \frac{1}{12}$
3	156				
4	268				
5	329	9	1	0.462	$\hat{\Lambda}(t_4) + \frac{1}{9}$
6	431	8	1	0.587	$\hat{\Lambda}(t_5) + \frac{1}{8}$
7	448	7	0	0.587	$\hat{\Lambda}(t_6) + \frac{0}{7}$
8	477	6	0	0.587	$\hat{\Lambda}(t_7) + \frac{0}{6}$
9	638	5	1	0.787	$\hat{\Lambda}(t_8) + \frac{1}{5}$
10	803	4	0		
11	855	3	0		
12	1040	2	0		
13	1106	1	0		

Question 18.7

Here are plots of the cumulative hazard (Nelson-Aalen estimator) for patients by sex and by ECOG performance score status:



Strata	0	300	600	900	1200
rx=1	13	9	5	2	0
rx=2	13	13	6	3	2

Strata	0	300	600	900	1200
ecog.ps=1	14	12	6	3	1
ecog.ps=2	12	10	5	2	1

How does treatment group appear to impact the cumulative hazard? What about ECOG score? Do the cumulative hazards appear proportional (i.e., related by a common multiplier) in each case?

18.3 Deriving the Cox Model

We have spent considerable time on the hazard and cumulative hazard because these play important roles in what is perhaps the most famous survival analysis tool: the Cox proportional hazards model ("Cox model", for short), developed by D.R. Cox in 1972. The model has the following form:

$$\lambda(t|x) = \lambda_0(t) \exp(\beta_1 x_1 + \beta_2 x_2 + \cdots + \beta_p x_p)$$

and another way of writing it is:

$$\log\left(\frac{\lambda(t|x)}{\lambda_0(t)}\right) = \beta_1 x_1 + \beta_2 x_2 + \cdots + \beta_p x_p.$$

Note that for now we are assuming that the covariates do not depend on time. There is a variant of the Cox model called the **extended Cox model** that allows time-dependent covariates. For now, we will just consider the fixed covariate case.

Question 18.8

Compare the Cox model to a logistic regression model. What is the same? What is different?

Here $\lambda_0(t)$ is called the **baseline hazard**. As usual, we symbolize the linear sum of the βs as $\beta^T x$. Importantly, the baseline hazard can take any shape as a function of time. The $\lambda_0(t)$ part of the equation is, therefore, referred to as the "nonparametric" part, while the $\beta^T x$ part is called the "parametric" part. The overall model is referred to as **semiparametric**.

The ratio of the hazards for two different sets of covariates, x and z, is

$$\frac{\lambda(t|x)}{\lambda(t|z)} = \frac{\lambda_0(t)\exp(\beta^T x)}{\lambda_0(t)\exp(\beta^T z)} = \exp(\beta^T(x-z)).$$

Taking the log of this, we arrive at

$$\log\left(\frac{\lambda(t|x)}{\lambda(t|z)}\right) = \beta^T(x-z).$$

A single coefficient, β_j, is therefore the **hazard ratio** when the corresponding predictor, x_j, increases by one. This ratio is assumed to be constant over time. The hazard ratio is also called the **relative risk**.

Question 18.9

Why doesn't the Cox model have an intercept, β_0?

Question 18.10

Compare the interpretation of the coefficients in a Cox model to their interpretation in a logistic regression model.

18.4 Fitting the Cox Model

Fitting a Cox model means taking a sample of possibly right-censored data and deriving estimates for the parameters, $\beta_1, \ldots, \beta_p$. Cox models are fit using a variant of maximum likelihood estimation called **partial likelihood estimation**.

Let's consider all of the unique times, t_i, that events are observed. For now, we will assume that exactly one event is observed at each of these times (no ties). We will use $R(t_i)$ to refer to the set of subjects who are "at risk" (i.e., not censored) just prior to time t_i. At each failure time, t_i, the contribution to the partial likelihood is:

$$\begin{aligned}\mathcal{L}_i(\beta) &= \frac{P(\text{person } i \text{ experiences event} \mid \text{still around at } t_i)}{\sum_{l \in R(t_i)} P(\text{person } l \text{ experiences event} \mid \text{still around at } t_i)} \\ &= \frac{\lambda(t_i|x_i)}{\sum_{l \in R(t_i)} \lambda(t_i|x_l)} = \frac{\exp(\beta^T x^{(i)})}{\sum_{l \in R(t_i)} \exp(\beta^T x^{(l)})}\end{aligned}$$

The complete partial likelihood over all K observed event times, $t_i = t_1, \ldots, t_K$, is:

$$\mathcal{L}(\beta) = \prod_{i=1}^{K} \frac{\exp(\beta^T x^{(i)})}{\sum_{l \in R(t_i)} \exp(\beta^T x^{(l)})}.$$

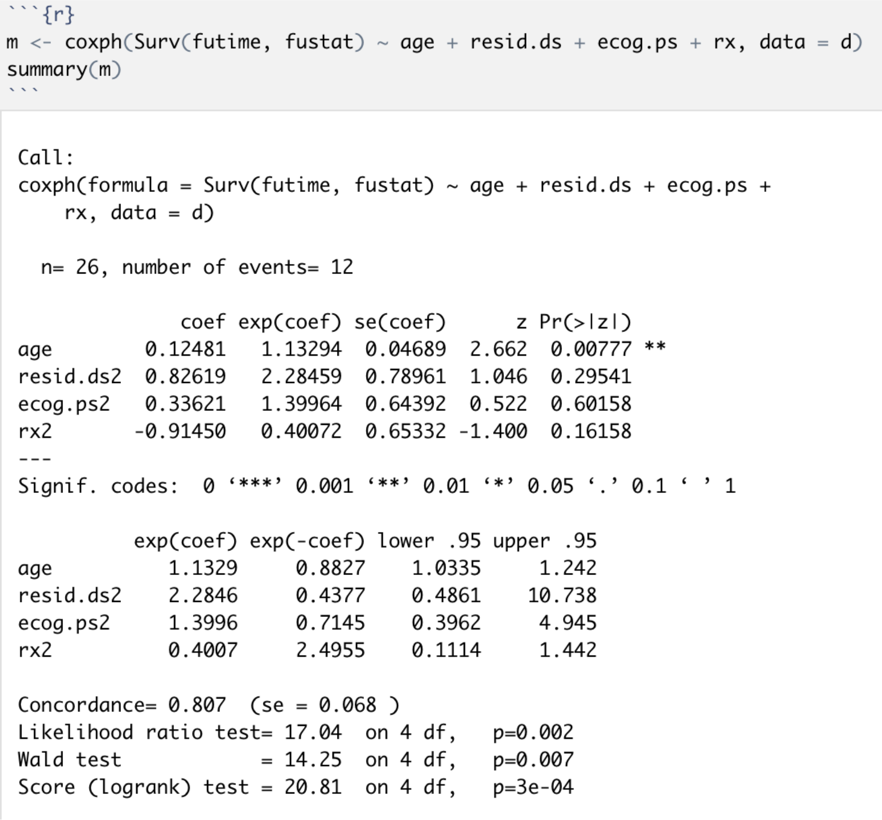
This is the thing that the model fitting process is trying to maximize. It is optimized numerically, using the same types of optimization procedures used by logistic regression and other generalized linear models.

Question 18.11

Why is this quantity called a "partial likelihood", instead of just a "likelihood"?

18.5 Interpreting Cox Models

Here is a simple Cox model for survival time vs. age, residual disease, ECOG score, and treatment group in the ovarian cancer dataset.



~~~
```{r}
m <- coxph(Surv(futime, fustat) ~ age + resid.ds + ecog.ps + rx, data = d)
summary(m)
```
~~~

```
Call:
coxph(formula = Surv(futime, fustat) ~ age + resid.ds + ecog.ps + 
    rx, data = d)

  n= 26, number of events= 12 

              coef exp(coef) se(coef)      z Pr(>|z|)   
age        0.12481   1.13294  0.04689  2.662  0.00777 **
resid.ds2  0.82619   2.28459  0.78961  1.046  0.29541   
ecog.ps2   0.33621   1.39964  0.64392  0.522  0.60158   
rx2       -0.91450   0.40072  0.65332 -1.400  0.16158   
---
Signif. codes:  0 ‘***’ 0.001 ‘**’ 0.01 ‘*’ 0.05 ‘.’ 0.1 ‘ ’ 1

          exp(coef) exp(-coef) lower .95 upper .95
age          1.1329     0.8827    1.0335     1.242
resid.ds2    2.2846     0.4377    0.4861    10.738
ecog.ps2     1.3996     0.7145    0.3962     4.945
rx2          0.4007     2.4955    0.1114     1.442

Concordance= 0.807  (se = 0.068 )
Likelihood ratio test= 17.04  on 4 df,   p=0.002
Wald test            = 14.25  on 4 df,   p=0.007
Score (logrank) test = 20.81  on 4 df,   p=3e-04
```

Question 18.12

Interpret the coefficients, exponentiated coefficients, standard errors of the coefficients, Z scores, and *p*-values in this model. Also try your hand at interpreting the second block of model output, which includes the exponentiated coefficients (again), the exponentiated negative coefficients, and the lower and upper bounds of a 95% confidence interval for the exponentiated coefficients.

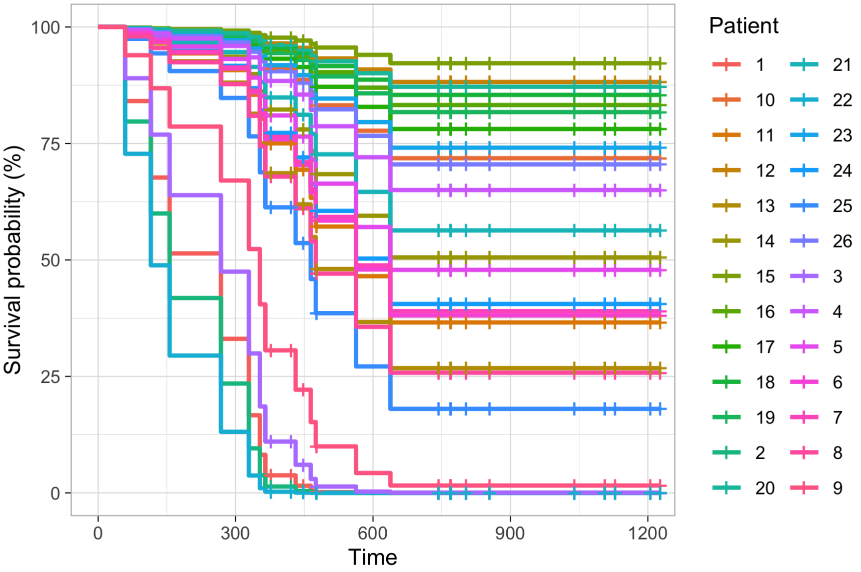
18.6 Making Predictions with Cox Models

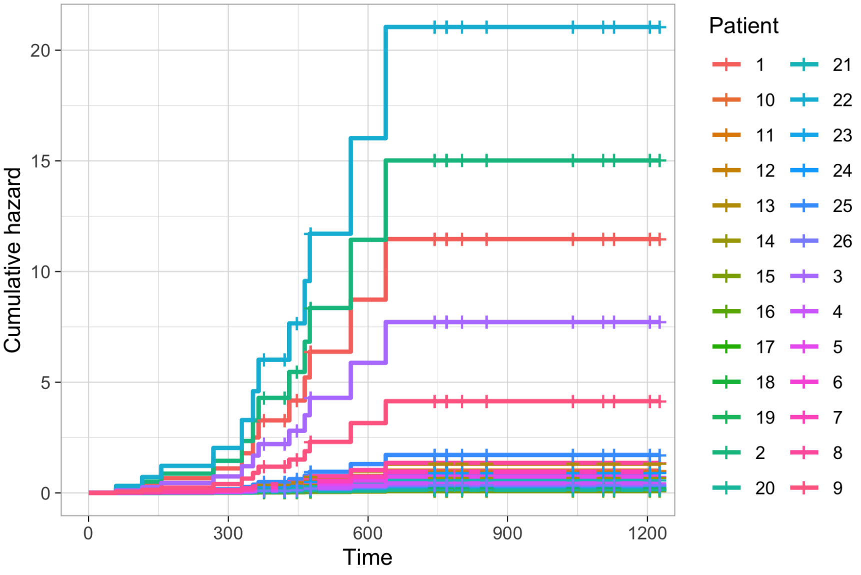
The Cox model fitted using the `coxph` function can be used to make various predictions on the original dataset. This yields a lot of output. All of the available outputs for the `ovarian` dataset are shown below.

	age	lp_age	resid.ds	lp_resid.ds	ecog.ps	lp_ecog.ps	rx	lp_rx	lp	risk	expected	surv
1	72.33	9.03	2	0.83	1	0.00	1	0.00	2.67	14.43	0.16	0.85
2	74.49	9.30	2	0.83	1	0.00	1	0.00	2.94	18.90	0.46	0.63
3	66.47	8.30	2	0.83	2	0.34	1	0.00	2.27	9.71	0.40	0.67
4	53.36	6.66	2	0.83	1	0.00	2	-0.91	-0.61	0.54	0.11	0.89
5	50.34	6.28	2	0.83	1	0.00	1	0.00	-0.08	0.93	0.25	0.78
6	56.43	7.04	1	0.00	2	0.34	1	0.00	0.19	1.21	0.33	0.72
7	56.94	7.11	2	0.83	2	0.34	2	-0.91	0.17	1.18	0.40	0.67
8	59.85	7.47	2	0.83	2	0.34	2	-0.91	0.53	1.71	0.70	0.49
9	64.18	8.01	2	0.83	1	0.00	1	0.00	1.65	5.21	2.15	0.12
10	55.18	6.89	1	0.00	2	0.34	2	-0.91	-0.88	0.42	0.24	0.79
11	56.76	7.08	1	0.00	2	0.34	1	0.00	0.24	1.27	0.94	0.39
12	50.11	6.25	1	0.00	1	0.00	2	-0.91	-1.84	0.16	0.12	0.89
13	59.63	7.44	2	0.83	2	0.34	2	-0.91	0.51	1.66	1.23	0.29
14	57.05	7.12	2	0.83	1	0.00	2	-0.91	-0.15	0.86	0.63	0.53
15	39.27	4.90	1	0.00	1	0.00	1	0.00	-2.28	0.10	0.08	0.93
16	43.12	5.38	1	0.00	2	0.34	1	0.00	-1.47	0.23	0.17	0.84
17	38.89	4.85	2	0.83	2	0.34	1	0.00	-1.17	0.31	0.23	0.79
18	44.60	5.57	1	0.00	1	0.00	1	0.00	-1.62	0.20	0.15	0.86
19	53.91	6.73	1	0.00	1	0.00	2	-0.91	-1.37	0.25	0.19	0.83
20	44.21	5.52	2	0.83	1	0.00	2	-0.91	-1.76	0.17	0.13	0.88
21	59.59	7.44	1	0.00	2	0.34	2	-0.91	-0.33	0.72	0.53	0.59
22	74.50	9.30	2	0.83	2	0.34	1	0.00	3.28	26.49	1.65	0.19
23	43.14	5.38	2	0.83	1	0.00	1	0.00	-0.97	0.38	0.04	0.96
24	63.22	7.89	1	0.00	2	0.34	2	-0.91	0.13	1.14	0.18	0.84
25	64.42	8.04	2	0.83	1	0.00	2	-0.91	0.77	2.16	0.45	0.64
26	58.31	7.28	1	0.00	1	0.00	2	-0.91	-0.82	0.44	0.09	0.91

The term `age` is the raw value for age for each patient, and the term `lp_age` is the linear predictor, $\beta_{\text{age}} x^{(i)}_{\text{age}}$, for patient i. The same is true for the other predictors. The term `lp` is the entire linear predictor, $\beta^T x$, for each $x^{(i)}$. Confusingly, it has been centered, so its value is shifted from the sum of columns 2, 4, 6, and 8 by a fixed amount (Exercise: What is this amount?). The `risk` term is just the overall risk score, exp(`lp`). The `expected` term is the expected number of events given the covariates and follow-up time. The survival probability, `surv`, for each subject is exp(−`expected`).

Cox models make no assumptions about the shape of the baseline hazard, so to make predictions, they simply use the empirical survival (or cumulative hazard) curve for the entire dataset and then adjust it up or down depending on the values of the covariates. The way R does this is super confusing - it estimates the baseline hazard at the means of the covariates after centering, so the baseline hazard is not very interpretable. You can get it out of the model using the `basehaz` function. In any case, here's what you get when you ask the model to predict the survival and cumulative hazard curves for all of the patients in the training set:





Question 18.13

Which patients have the lowest and highest risk scores? Where do they appear on the patient-level survival and cumulative hazard graphs?

18.7 Testing the Proportional Hazards Assumption

The Cox model makes three important assumptions:

1. *Common baseline hazard.* At any time, t, all individuals experience the same baseline hazard, $\lambda_0(t)$.
2. *Proportional hazards.* The hazard for one individual is proportional to the hazard of any other individual.
3. *Time-invariance.* The constant of proportionality between the hazards of any two individuals does not depend on time.

All of them are potentially problematic. In particular, it's hard to come up with situations in which the hazards for *any* two individuals can reasonably be assumed to be proportional. Thus, it's important to check this assumption.

There are whole book chapters and papers devoted to model diagnostics for the Cox model. I will present a couple of common methods here and leave the others to the course website.

18.7.1 Schoenfeld Residuals

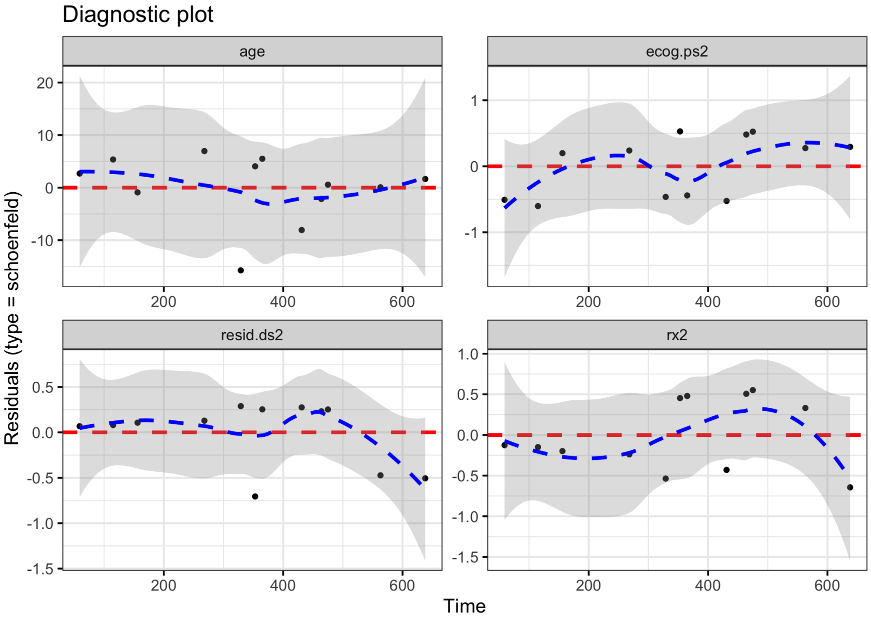
In Section 18.4, we saw how the Cox model was fit using maximization of the partial likelihood. The quantity

$$\frac{\exp(\beta^T x^{(i)})}{\sum_{l \in R(t_i)} \exp(\beta^T x^{(l)})}$$

was important because it gave us the probability, according to the model, that the person observed to experience the event at time t_i would experience it, given all the people in the risk set just prior to time t_i. The **Schoenfeld residual** capitalizes on this idea.

> **Schoenfeld residual:** The covariate value $x_j^{(i)}$ for the person (i) who actually experienced the event at time t_i, minus the expected value of the covariate for the risk set at t_i. Or:
>
> $$\text{residual} = x_j^{(i)} - \sum_{l \in R(t_i)} x_j^{(l)} \frac{\exp(\beta^T x^{(l)})}{\sum_{m \in R(t_i)} \exp(\beta^T x^{(m)})}$$

There is one Schoenfeld residual for each combination of observed event and covariate. Typically, they will be plotted against time to assess if there is a trend. The test for trend comes from a simple linear regression model of the residuals against time, conducted separately for each covariate.



Question 18.14

How would you conduct the test for trend for each covariate using a simple linear regression model?

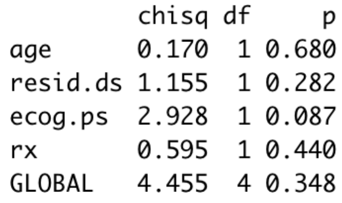
Question 18.15

Try calculating the Schoenfeld residual for a single covariate and failure time (your choice). All of the information you need is in the table below. The `risk` column is the same as in the previous table. It is $\exp(\beta^T x)$.

	futime	fustat	age	resid.ds	ecog.ps	rx	risk
1	59	1	72.33	2	1	1	14.43
2	115	1	74.49	2	1	1	18.90
3	156	1	66.47	2	2	1	9.71
22	268	1	74.50	2	2	1	26.49
23	329	1	43.14	2	1	1	0.38
24	353	1	63.22	1	2	2	1.14
25	365	1	64.42	2	1	2	2.16
26	377	0	58.31	1	1	2	0.44
4	421	0	53.36	2	1	2	0.54
5	431	1	50.34	2	1	1	0.93
6	448	0	56.43	1	2	1	1.21
7	464	1	56.94	2	2	2	1.18
8	475	1	59.85	2	2	2	1.71
9	477	0	64.18	2	1	1	5.21
10	563	1	55.18	1	2	2	0.42
11	638	1	56.76	1	2	1	1.27
12	744	0	50.11	1	1	2	0.16
13	769	0	59.63	2	2	2	1.66
14	770	0	57.05	2	1	2	0.86
15	803	0	39.27	1	1	1	0.10
16	855	0	43.12	1	2	1	0.23
17	1040	0	38.89	2	2	1	0.31
18	1106	0	44.60	1	1	1	0.20
19	1129	0	53.91	1	1	2	0.25
20	1206	0	44.21	2	1	2	0.17
21	1227	0	59.59	1	2	2	0.72

Question 18.16

The R function `cox.zph` performs the test of trend for all predictors as well as a global test of trend using ANOVA (don't worry, we'll get to this later). Here is the output for this model:



```
         chisq df     p
age      0.170  1 0.680
resid.ds 1.155  1 0.282
ecog.ps  2.928  1 0.087
rx       0.595  1 0.440
GLOBAL   4.455  4 0.348
```

For which predictors is there a potentially worrying association between the Schoenfeld residuals and time?

18.7.2 What to do if Violations are Found

Interpretation of the Cox model is relatively insensitive to deviations from proportionality, especially for large sample sizes. However, if nonproportionality is a huge issue for one or more predictors, there are a few strategies to deal with it.

1. *Stratify.* One can stratify the model by different levels of the problematic predictor(s), essentially building separate models for the other covariates at each different level of the problematic predictor(s). This only works for predictors that have discrete levels, however; otherwise, one would need to discretize. A potential downside is that stratification eliminates the model's ability to quantify the effect of the stratification variable(s).

2. *Partition the time axis.* Sometimes proportionality holds for the first part of the time axis but falls apart at the end. In that case, one can analyze the data from the first part of the study separately. The disadvantage, of course, is that one must throw out information from later parts of the study.

3. *Add a nonlinear effect term.* Continuous covariates with nonlinear effects on the outcome may lead to nonproportional hazards. Including transformations of these covariates may help to alleviate the nonproportional hazards.

Chapter 19

Survival Trees

19.1 The Log-Rank Test

The **log-rank test** (Mantel 1966; Peto and Peto 1972) is a test for statistical equivalence of two survival curves. It is obtained by constructing a $2x2$ contingency table at the time of each event and comparing the failure rates between the two groups, conditional on the number at risk in each group[1]. In this way, the test compares the entire survival experience between groups. The null hypothesis is that the true underlying curves for the two groups are identical.

"In the absence of censoring, these methods reduce to the Wilcoxon-Mann-Whitney rank-sum test (Mann and Whitney 1947) for two samples and to the Kruskal-Wallis test (Kruskal and Wallis 1952) for more than two groups of survival times."

19.2 Survival Example: Primary Biliary Cirrhosis

Now let's consider how the same tree-building machinery

This data is from the Mayo Clinic trial in primary biliary cirrhosis (PBC) of the liver conducted between 1974 and 1984. A total of 424 PBC patients,

[1] See https://bookdown.org/sestelo/sa_financial/comparing-survival-curves.html.

referred to Mayo Clinic during that ten-year interval, met eligibility criteria for the randomized placebo controlled trial of the drug D-penicillamine. The first 312 cases in the data set participated in the randomized trial and contain largely complete data. The additional 112 cases did not participate in the clinical trial, but consented to have basic measurements recorded and to be followed for survival. Six of those cases were lost to follow-up shortly after diagnosis, so the data here are on an additional 106 cases as well as the 312 randomized participants.

Question 19.1

Here's a dataset of survival data... how would you build a survival forest?

19.3 Random Survival Forests

19.4 Boosted Survival Trees