# Regression Models for Epidemiology

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## **Preface**

This web-book is derived from my lecture slides for the Spring 2023 session of Epidemiology 204: "Quantitative Epidemiology III: Statistical Models", at UC Davis.

I have drawn these materials from many sources, including but not limited to:

- David Rocke<sup>1</sup>'s materials from the 2021 edition of Epi 204<sup>2</sup>
- Regression methods in biostatistics: linear, logistic, survival, and repeated measures models, 2nd edition (Vittinghoff et al. 2012)
- An Introduction to Generalized Linear Models, 4th edition (Dobson and Barnett 2018)

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The code samples in this book are licensed under Creative Commons CC0  $1.0 \text{ Universal (CC0 } 1.0)^4$ , i.e. public domain.

<sup>&</sup>lt;sup>1</sup>https://dmrocke.ucdavis.edu/

<sup>&</sup>lt;sup>2</sup>https://dmrocke.ucdavis.edu/Class/EPI204-Spring-2021/EPI204-Spring-2021.html

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<sup>&</sup>lt;sup>4</sup>https://creativecommons.org/publicdomain/zero/1.0/

#### Configuring R

Functions from these packages will be used throughout this document:

```
library(ggplot2) # graphics
library(ggeasy) # help with graphics
library(plotly) # interactive graphics
library(dplyr) # manipulate data
library(tidyr) # Tools to help to create tidy data
library(haven) # import Stata files
library(pander) # format tables for markdown
library(knitr) # format R output for markdown
library(kableExtra) # more markdown formatting
library(parameters) # format model output tables for markdown
library(reactable) # interactive tables
library(dobson) # datasets from Dobson and Barnett 2018
library(conflicted) # check for conflicting function definitions
```

Here are some R settings I use in this document:

```
rm(list = ls()) # delete any data that's already loaded into R
knitr::opts_chunk$set(message = FALSE)
knitr::opts_chunk$set(warning = FALSE)
pander::panderOptions("table.emphasize.rownames", FALSE)
options('digits' = 4)
```

```
conflicts_prefer(plotly::filter)
conflicts_prefer(ggplot2::autoplot)
```

## 1.1. Introduction to Epi 204

Welcome to Epidemiology 204: Quantitative Epidemiology III (Statistical Models).

In this course, we will start where Epi 203 left off: with linear regression models

#### Note

Epi 203/STA 130B/STA 131B is a prerequisite for this course. If you haven't passed one of these courses, please talk to me after class.

#### 1.1.1. What you should know

Epi 202: probability models for different data types

- binomial
- Poisson
- Gaussian
- exponential

Epi 203: inference for one or several homogenous populations

- the maximum likelihood inference framework:
  - likelihood functions
  - log-likelihood functions
  - score functions

- estimating equations
- information matrices
- point estimates
- standard errors
- confidence intervals
- hypothesis tests
- p-values
- Hypothesis tests for one, two, and >2 groups:
  - t-tests/ANOVA for Gaussian models
  - chi-square tests for binomial and Poisson models
- Some linear regression

Stat 108: linear regression models

- building models for Gaussian outcomes
  - multiple predictors
  - interactions
- regression diagnostics
- fundamentals of R programming; e.g.:
  - Wickham, Çetinkaya-Rundel, and Grolemund (2023)
  - Dalgaard (2008)
- RMarkdown or Quarto for formatting homework<sup>1</sup>
  - LaTeX for writing math in RMarkdown/Quarto

#### 1.1.2. What we will cover in this course

• Linear (Gaussian) regression models (review and more details)

<sup>&</sup>lt;sup>1</sup>https://r4ds.hadley.nz/quarto

- Regression models for non-Gaussian outcomes
  - binary
  - count
  - time to event
- Statistical analysis using R

## 1.2. Regression models

Why do we need them?

- continuous predictors
- not enough data to analyze some subgroups individually

## 1.2.1. Example: Adelie penguins

```
library(ggplot2)
library(plotly)
library(dplyr)
ggpenguins <-
   palmerpenguins::penguins |>
   dplyr::filter(species == "Adelie") |>
   ggplot(
    aes(x = bill_length_mm , y = body_mass_g)) +
   geom_point() +
   xlab("Bill length (mm)") +
   ylab("Body mass (g)")
```

## ggpenguins |> print()



Figure 1.1.: Palmer penguins

## 1.2.2. Linear regression

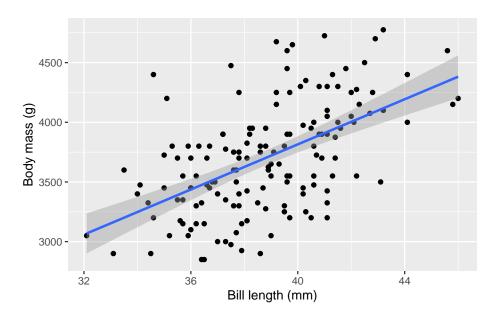
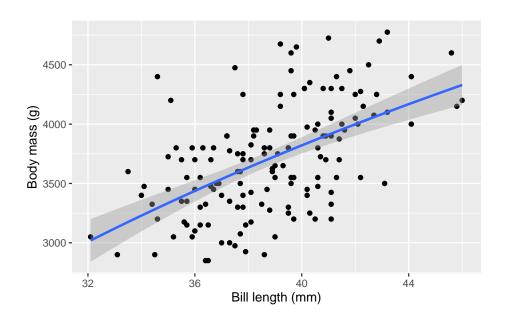


Figure 1.2.: Palmer penguins with linear regression fit

## 1.2.3. Curved regression lines

```
ggpenguins2 = ggpenguins +
  stat_smooth(
    method = "lm",
    formula = y ~ log(x),
    geom = "smooth") +
  xlab("Bill length (mm)") +
  ylab("Body mass (g)")
```

## ggpenguins2 |> print()

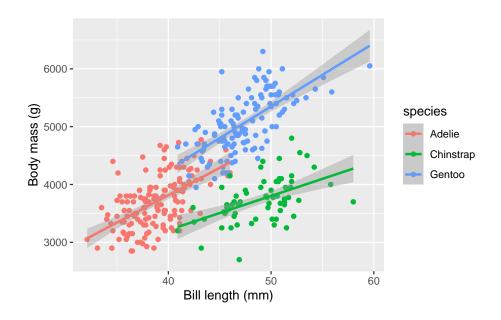


## 1.2.4. Multiple regression

```
ggpenguins =
  palmerpenguins::penguins |>
  ggplot(
   aes(x = bill_length_mm ,
       y = body_mass_g,
       color = species
  )
  ) +
  geom_point() +
```

```
stat_smooth(
  method = "lm",
  formula = y ~ x,
  geom = "smooth") +
xlab("Bill length (mm)") +
ylab("Body mass (g)")
```

## ggpenguins |> print()



## 1.2.5. Modeling non-Gaussian outcomes

```
library(glmx)
data(BeetleMortality)
```

```
beetles = BeetleMortality |>
  mutate(
    pct = died/n,
    survived = n - died
)

plot1 =
  beetles |>
  ggplot(aes(x = dose, y = pct)) +
  geom_point(aes(size = n)) +
    xlab("Dose (log mg/L)") +
    ylab("Mortality rate (%)") +
  scale_y_continuous(labels = scales::percent) +
  # xlab(bquote(log[10]), bquote(CS[2])) +
  scale_size(range = c(1,2))
```

```
print(plot1)
```



Figure 1.3.: Mortality rates of adult flour beetles after five hours' exposure to gaseous carbon disulphide (Bliss 1935)

## 1.2.6. Why don't we use linear regression?

```
beetles_long =
  beetles |>
  reframe(.by = everything(),
      outcome = c(
      rep(1, times = died),
      rep(0, times = survived))
)
```

```
beetles_long |>
lm(
   formula = outcome ~ dose,
   data = _)

range1 = range(beetles$dose) + c(-.2, .2)

f.linear = function(x) predict(lm1, newdata = data.frame(dose = x))

plot2 =
   plot1 +
   geom_function(fun = f.linear, aes(col = "Straight line")) +
   labs(colour="Model", size = "")

print(plot2)
```



Figure 1.4.: Mortality rates of adult flour beetles after five hours' exposure to gaseous carbon disulphide (Bliss 1935)

## 1.2.7. Zoom out

```
print(plot2 + expand_limits(x = c(1.6, 2)))
```

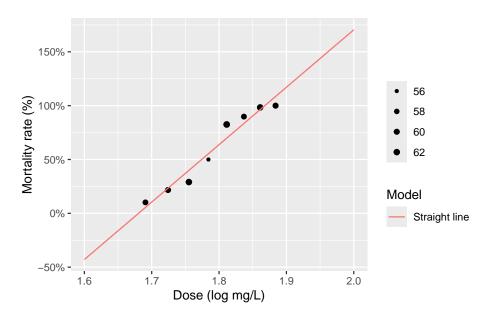


Figure 1.5.: Mortality rates of adult flour beetles after five hours' exposure to gaseous carbon disulphide (Bliss 1935)

## 1.2.8. log transformation of dose?

```
lm2 =
  beetles_long |>
  lm(formula = outcome ~ log(dose), data = _)

f.linearlog = function(x) predict(lm2, newdata = data.frame(dose = x))

plot3 = plot2 +
```

```
expand_limits(x = c(1.6, 2)) +
geom_function(fun = f.linearlog, aes(col = "Log-transform dose"))
print(plot3 + expand_limits(x = c(1.6, 2)))
```

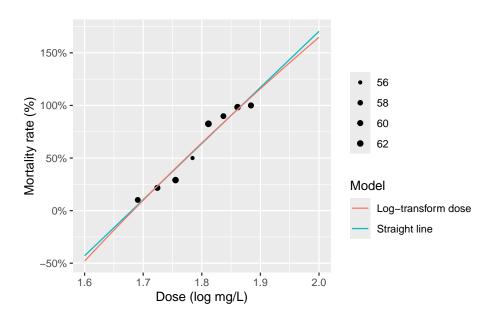


Figure 1.6.: Mortality rates of adult flour beetles after five hours' exposure to gaseous carbon disulphide (Bliss 1935)

## 1.2.9. Logistic regression

```
glm1 = beetles |>
  glm(formula = cbind(died, survived) ~ dose, family = "binomial")
```

```
f = function(x) predict(glm1, newdata = data.frame(dose = x), type = "response")
plot4 = plot3 + geom_function(fun = f, aes(col = "Logistic regression"))
print(plot4)
```

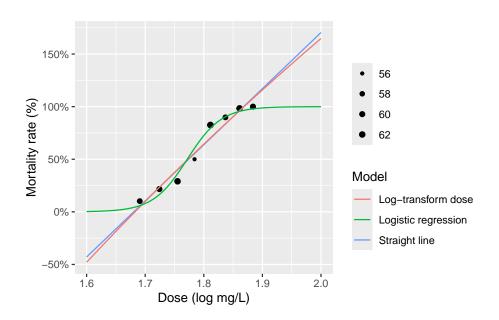


Figure 1.7.: Mortality rates of adult flour beetles after five hours' exposure to gaseous carbon disulphide (Bliss 1935)

#### 1.2.10. Three parts to regression models

• What distribution does the outcome have for a specific subpopulation defined by covariates? (outcome model)

- How does the combination of covariates relate to the mean? (link function)
- How do the covariates combine? (linear predictor, interactions)

#### 1.3. Other resources

These notes represent my still-developing perspective on regression models in epidemiology. Many other statisticians and epidemiologists have published their own perspectives, and you are encouraged to explore your many options and find ones that resonate with you. I have attempted to cite my sources throughout these notes. Here are some additional resources:

- Dunn, Smyth, et al. (2018) is a recent textbook on GLMs. It doesn't cover time-to-event models, and it doesn't use the modern tidyverse<sup>2</sup> packages (ggplot2<sup>3</sup>, dplyr<sup>4</sup>, etc.), but otherwise it seems great.
- Moore (2016) is a recent textbook on survival analysis. It also doesn't use the tidyverse, but otherwise seems great.
- https://online.stat.psu.edu/stat504/book/ provides course notes for "STAT 504 Analysis of Discrete Data" at Penn State University. It includes logistic regression and Poisson regression, as well as 2-way tables and other related topics, and includes SAS code.

<sup>&</sup>lt;sup>2</sup>https://tidyverse.org/

<sup>&</sup>lt;sup>3</sup>https://ggplot2.tidyverse.org/

<sup>&</sup>lt;sup>4</sup>https://dplyr.tidyverse.org/

# Part I. Generalized Linear Models

This section is primarily adapted starting from the textbook "An Introduction to Generalized Linear Models" (4th edition, 2018) by Annette J. Dobson and Adrian G. Barnett:

#### https://doi.org/10.1201/9781315182780

The type of predictive model one uses depends on several issues; one is the type of response.

- Measured values such as quantity of a protein, age, weight usually can be handled in an ordinary linear regression model, possibly after a log transformation.
- Patient survival, which may be censored, calls for a different method (survival analysis, Cox regression).
- If the response is binary, then can we use logistic regression models
- If the response is a count, we can use Poisson regression
- If the count has a higher variance than is consistent with the Poisson, we can use a negative binomial or over-dispersed Poisson
- Other forms of response can generate other types of generalized linear models

We need a linear predictor of the same form as in linear regression x. In theory, such a linear predictor can generate any type of number as a prediction, positive, negative, or zero

We choose a suitable distribution for the type of data we are predicting (normal for any number, gamma for positive numbers, binomial for binary responses, Poisson for counts)

We create a link function which maps the mean of the distribution onto the set of all possible linear prediction results, which is the whole real line  $(-\infty, \infty)$ . The inverse of the link function takes the linear predictor to the actual prediction.

- Ordinary linear regression has identity link (no transformation by the link function) and uses the normal distribution
- If one is predicting an inherently positive quantity, one may want to use the log link since ex is always positive.
- An alternative to using a generalized linear model with a log link, is to transform the data using the log. This is a device that works well with measurement data and may be usable in other cases, but it cannot be used for 0/1 data or for count data that may be 0.

Table 1.1.: R glm() Families

	5()
Family	Links
gaussian	identity, log, inverse
binomial	logit, probit, cauchit, log, cloglog
gamma	inverse, identity, log
inverse.gaussian	1/mu^2, inverse, identity, log
Poisson	log, identity, sqrt
quasi	identity, logit, probit, cloglog,
	inverse, log, 1/mu^2 and sqrt
quasibinomial	logit, probit, identity, cloglog,
	inverse, log, 1/mu^2 and sqrt
quasipoisson	log, identity, logit, probit, cloglog,
	inverse, $1/mu^2$ and sqrt

Table 1.2.: R glm() Link Functions;  $\eta = X\beta = g(\mu)$ 

Name	Domain	Range	Link Function	Inverse Link Function
identity	$(-\infty,\infty)$	$(-\infty,\infty)$	$\eta = \mu$	$\mu = \eta$
$\log$	$(0, \infty)$	$(-\infty, \infty)$	$\eta = \log \{\mu\}$	$\mu = \exp\left\{\eta\right\}$
inverse	$(0, \infty)$	$(0,\infty)$	$\eta = 1/\mu$	$\mu = 1/\eta$

			Link	Inverse Link
Name	Domain	Range	Function	Function
logit	(0,1)	$(-\infty, \infty)$	$\eta =$	$\mu =$
			$\log \left\{ \mu/(1 -$	$(\mu) \exp \{\eta\} / (1 +$
				$\exp\left\{\eta ight\}$
probit	(0, 1)	$(-\infty,\infty)$	$\eta =$	$\mu = \Phi(\eta)$
			$\Phi^{-1}(\mu)$	
cloglog	(0, 1)	$(-\infty, \infty)$	$\eta =$	$\mu =$
			$\log \left\{ -\log \left\{ 1\right\} \right\}$	$1 - 1\mu$ $\exp {-\exp {}$
1/mu^2	$(0,\infty)$	$(0,\infty)$		$\mu = 1/\sqrt{\eta}$
$\operatorname{sqrt}$	$(0,\infty)$	$(0,\infty)$	$\eta = \sqrt{\mu}$	$\mu = \eta^2$

#### Note

This content is adapted from:

- Dobson and Barnett (2018), Chapters 2-6
- Dunn, Smyth, et al. (2018), Chapters 2-3
- Vittinghoff et al. (2012), Chapter 4

There are numerous textbooks specifically for linear regression, including:

- Kutner et al. (2005): used for UCLA Biostatistics MS level linear models class
- Chatterjee and Hadi (2015): used for Stanford MS-level linear models class
- Seber and Lee (2012): used for UCLA Biostatistics PhD level linear models class
- Kleinbaum et al. (2014): same first author as Kleinbaum and Klein (2010) and Kleinbaum and Klein (2012)

Functions from these packages will be used throughout this document:

```
library(knitr) # compiling .qmd files
library(pander) # format tables for markdown
library(ggplot2) # graphics
library(ggeasy) # help with graphics:
```

```
# - `ggeasy::easy_labs()` applies same logic as `ggplot2::labs()` but uses as defaul
library(dplyr) # manipulate data
library(haven) # import Stata files
library(tidyr) # Tools to help to create tidy data
library(plotly) # interactive graphics
library(dobson) # datasets from Dobson and Barnett 2018
library(parameters) # format model output tables for markdown
library(conflicted) # check for conflicting function definitions
library(magrittr) # `%>%` and other additional piping tools
```

#### 2.1. Overview

#### 2.1.1. Why this course includes linear regression

- This course is about *generalized linear models* (for non-Gaussian outcomes)
- UC Davis STA 108 ("Applied Statistical Methods: Regression Analysis") is a prerequisite for this course, so everyone here should have some understanding of linear regression already.
- We will review linear regression to:
  - make sure everyone is caught up
  - to provide an epidemiological perspective on model interpretation.

#### 2.1.2. Chapter overview

- Section 2.2: how to interpret linear regression models
- Section 2.3: how to estimate linear regression models

- Section 2.4: how to quantify uncertainty about our estimates
- Section 2.8: how to tell if your model is insufficiently complex

# 2.2. Understanding Gaussian Linear Regression Models

#### 2.2.1. Motivating example: birthweights and gestational age

Suppose we want to learn about the distributions of birthweights ( $outcome\ Y$ ) for (human) babies born at different gestational ages ( $covariate\ A$ ) and with different chromosomal sexes ( $covariate\ S$ ) (Dobson and Barnett (2018) Example 2.2.2).

#### 2.2.1.1. Data as table

```
library(dobson)
data("birthweight", package = "dobson")
birthweight |> knitr::kable()
```

Table 2.1.: birthweight data (Dobson and Barnett (2018) Example 2.2.2)

boys gestational age	boys weight	girls gestational age	girls weight
40	2968	40	3317
38	2795	36	2729
40	3163	40	2935
35	2925	38	2754
36	2625	42	3210
37	2847	39	2817
41	3292	40	3126

Table 2.1.: birthweight data (Dobson and Barnett (2018) Example 2.2.2)

boys gestational age	boys weight	girls gestational age	girls weight
40	3473	37	2539
37	2628	36	2412
38	3176	38	2991
40	3421	39	2875
38	2975	40	3231

#### 2.2.1.2. Reshape data for graphing

```
bw =
  birthweight |>
  pivot_longer(
    cols = everything(),
    names_to = c("sex", ".value"),
    names_sep = "s "
) |>
  rename(age = `gestational age`) |>
  mutate(
    sex = sex |>
        case_match(
        "boy" ~ "male",
        "girl" ~ "female") |>
        factor(levels = c("female", "male")))
```

Table 2.2.: birthweight data reshaped

sex	age	weight
male	40	2968
female	40	3317
male	38	2795
female	36	2729
male	40	3163
female	40	2935
male	35	2925
female	38	2754
male	36	2625
female	42	3210
male	37	2847
female	39	2817
male	41	3292
female	40	3126
male	40	3473
female	37	2539
male	37	2628
female	36	2412
male	38	3176
female	38	2991
male	40	3421
female	39	2875
male	38	2975
female	40	3231

## 2.2.1.3. Data as graph

```
plot1 = bw |>
  ggplot(aes(
```

```
x = age,
y = weight,
linetype = sex,
shape = sex,
col = sex)) +
theme_bw() +
xlab("Gestational age (weeks)") +
ylab("Birthweight (grams)") +
theme(legend.position = "bottom") +
# expand_limits(y = 0, x = 0) +
geom_point(alpha = .7)
print(plot1 + facet_wrap(~ sex))
```



Figure 2.1.: birthweight data (Dobson and Barnett (2018) Example 2.2.2)

#### 2.2.1.4. Data notation

Let's define some notation to represent this data.

- Y: birthweight (measured in grams)
- S: chromosomal sex: "male" (XY) or "female" (XX)
- M: indicator variable for S = "male"<sup>1</sup>

 $<sup>^{-1}</sup>M$  is implicitly a deterministic function of S

- -M = 0 if female (XX) -M = 1 if male (XY)
- F: indicator variable for  $S = \text{"female"}^2$ 
  - -F = 1 if female (XX) -F = 0 if male (XY)
- A: estimated gestational age at birth (measured in weeks).

#### Note

Female is the **reference level** for the categorical variable S (chromosomal sex) and corresponding indicator variable M. The choice of a reference level is arbitrary and does not limit what we can do with the resulting model; it only makes it more computationally convenient to make inferences about comparisons involving that reference group.

#### 2.2.2. Parallel lines regression

We don't have enough data to model the distribution of birth weight separately for each combination of gestational age and sex, so let's instead consider a (relatively) simple model for how that distribution varies with gestational age and sex:

$$\begin{split} p(Y=y|A=a,S=s) &\sim_{\mathrm{iid}} N(\mu(a,s),\sigma^2) \\ &\mu(a,s) \stackrel{\mathrm{def}}{=} \mathbb{E}\left[Y|A=a,S=s\right] \\ &= \beta_0 + \beta_A a + \beta_M m \end{split} \tag{2.1}$$

 $<sup>{}^2</sup>F$  is implicitly a deterministic function of S

Table 2.3 shows the parameter estimates from R. Figure 2.2 shows the estimated model, superimposed on the data.

```
bw_lm1 = lm(
  formula = weight ~ sex + age,
  data = bw)

bw_lm1 |>
  parameters() |>
  print_md(
    include_reference = TRUE,
    # show_sigma = TRUE,
    select = "{estimate}")
```

Table 2.3.: Estimate of Equation 2.1 for birthweight data

Parameter	Estimate
(Intercept)	-1773.32
sex (female)	0.00
sex (male)	163.04
age	120.89

```
bw =
  bw |>
  mutate(`E[Y|X=x]` = fitted(bw_lm1)) |>
  arrange(sex, age)

plot2 =
  plot1 %+% bw +
  geom_line(aes(y = `E[Y|X=x]`))

print(plot2)
```

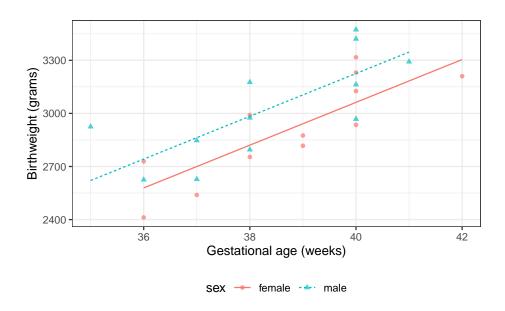


Figure 2.2.: Parallel-slopes model of birthweight

#### 2.2.2.1. Model assumptions and predictions

To learn what this model is assuming, let's plug in a few values.

Exercise 2.1. According to this model, what's the mean birthweight for a female born at 36 weeks?

```
coef(bw_lm1)
#> (Intercept) sexmale age
#> -1773.32184 163.03930 120.89433
```

\_\_\_\_\_

Solution.

$$\begin{split} E[Y|A=0, A=36] &= \beta_0 + \beta_M \cdot 0 + \beta_A \cdot 36 \\ &= 2578.873934 \end{split}$$

Exercise 2.2. What's the mean birthweight for a male born at 36 weeks?

\_\_\_\_\_

Solution.

$$\begin{split} E[Y|A=1,A=36] &= \beta_0 + \beta_M \cdot 1 + \beta_A \cdot 36 \\ &= 2741.91323693 \end{split}$$

Exercise 2.3. What's the difference in mean birthweights between males born at 36 weeks and females born at 36 weeks?

```
coef(bw_lm1)
#> (Intercept) sexmale age
#> -1773.3 163.0 120.9
```

Solution.

$$E[Y|M = 1, A = 36] - E[Y|M = 0, A = 36]$$
  
= 2741.91323693 - 2578.873934  
= 163.03930293

Shortcut:

$$\begin{split} E[Y|A=1,A=36] - E[Y|A=0,A=36] \\ &= (\beta_0 + \beta_M \cdot 1 + \beta_A \cdot 36) - (\beta_0 + \beta_M \cdot 0 + \beta_A \cdot 36) \\ &= \beta_M \\ &= 163.03930293 \end{split}$$

Note that age doesn't show up in this difference: in other words, according to this model, the difference between females and males with the same gestational age is the same for every age.

That's an assumption of the model; it's built-in to the parametric structure, even before we plug in the estimated values of those parameters.

That's why the lines are parallel.

#### 2.2.3. Interactions

What if we don't like that parallel lines assumption?

Then we need to allow an "interaction" between age A and sex S:

$$E[Y|A = a, S = s] = \beta_0 + \beta_A a + \beta_M m + \beta_{AM} (a \cdot m)$$
 (2.2)

Now, the slope of mean birthweight E[Y|A,S] with respect to gestational age A depends on the value of sex S.

```
bw_lm2 = lm(weight ~ sex + age + sex:age, data = bw)
bw_lm2 |>
  parameters() |>
  print_md(
    include_reference = TRUE,
    # show_sigma = TRUE,
    select = "{estimate}")
```

Table 2.4.: Birthweight model with interaction term

Parameter	Estimate
(Intercept)	-2141.67
sex (female)	0.00
sex (male)	872.99
age	130.40
$sex (male) \times age$	-18.42

```
bw =
  bw |>
  mutate(
    predlm2 = predict(bw_lm2)
) |>
  arrange(sex, age)

plot1_interact =
  plot1 %+% bw +
  geom_line(aes(y = predlm2))

print(plot1_interact)
```



Figure 2.3.: Birthweight model with interaction term

Now we can see that the lines aren't parallel.

Here's another way we could rewrite this model (by collecting terms involving S):

$$E[Y|A, S] = \beta_0 + \beta_A A + (\beta_M + \beta_{AM} A)M$$

#### Note

If you want to understand a coefficient in a model with interactions, collect terms for the corresponding variable, and you will see what other variables are interacting with the variable you are interested in.

In this case, the coefficient S is interacting with A. So the slope of Y with respect to  $X_2$  depends on the value of  $X_2$ .

According to this model, there is no such thing as "the slope of birthweight with respect to age". There are two slopes, one for each sex.<sup>3</sup> We can only talk about "the slope of birthweight with respect to age among males" and "the slope of birthweight with respect to age among females".

Then: that coefficient is the difference in means per unit change in its corresponding coefficient, when the other collected variables are set to 0.

To learn what this model is assuming, let's plug in a few values.

Exercise 2.4. According to this model, what's the mean birthweight for a female born at 36 weeks?

\_\_\_\_

Solution.

<sup>&</sup>lt;sup>3</sup>using the definite article "the" would mean there is only one slope.

$$E[Y|A=0,X_2=36] = \beta_0 + \beta_M \cdot 0 + \beta_A \cdot 36 + \beta_{AM} \cdot (0*36) = 2552.733333333$$

Exercise 2.5. What's the mean birthweight for a male born at 36 weeks?

Solution.

```
pred_male =
  coef(bw_lm2)["(Intercept)"] +
  coef(bw_lm2)["sexmale"] +
  coef(bw_lm2)["age"]*36 +
  coef(bw_lm2)["sexmale:age"] * 36
```

$$\begin{split} E[Y|A=0, X_2=36] &= \beta_0 + \beta_M \cdot 1 + \beta_A \cdot 36 + \beta_{AM} \cdot 1 \cdot 36 \\ &= 2762.70689655 \end{split}$$

Exercise 2.6. What's the difference in mean birthweights between males

born at 36 weeks and females born at 36 weeks?

Solution.

$$\begin{split} E[Y|M=1,A=36] - E[Y|M=0,A=36] \\ &= (\beta_0 + \beta_M \cdot 1 + \beta_A \cdot 36 + \beta_{AM} \cdot 1 \cdot 36) \\ &- (\beta_0 + \beta_M \cdot 0 + \beta_A \cdot 36 + \beta_{AM} \cdot 0 \cdot 36) \\ &= \beta_S + \beta_{AM} \cdot 36 \\ &= 209.97356322 \end{split}$$

Note that age now does show up in the difference: in other words, according to this model, the difference in mean birthweights between females and males with the same gestational age can vary by gestational age.

That's how the lines in the graph ended up non-parallel.

#### 2.2.4. Stratified regression

We could re-write the interaction model as a stratified model, with a slope and intercept for each sex:

$$\mathbb{E}[Y|A=a,S=s] = \beta_M m + \beta_{AM}(a \cdot m) + \beta_F f + \beta_{AF}(a \cdot f)$$
 (2.3)

Compare this stratified model with our interaction model, Equation 2.2:

$$\mathbb{E}[Y|A=a,S=s] = \beta_0 + \beta_A a + \beta_M m + \beta_{AM}(a \cdot m)$$

In the stratified model, the intercept term  $\beta_0$  has been relabeled as  $\beta_F$ .

```
bw_lm2 = lm(weight ~ sex + age + sex:age, data = bw)
bw_lm2 |>
  parameters() |>
  print_md(
   include_reference = TRUE,
```

```
# show_sigma = TRUE,
select = "{estimate}")
```

Table 2.5.: Birthweight model with interaction term

Parameter	Estimate
(Intercept)	-2141.67
sex (female)	0.00
sex (male)	872.99
age	130.40
$\mathrm{sex}\ (\mathrm{male})\times\mathrm{age}$	-18.42

```
bw_lm_strat =
  bw |>
  lm(
    formula = weight ~ sex + sex:age - 1,
    data = _)

bw_lm_strat |>
  parameters() |>
  print_md(
    # show_sigma = TRUE,
    select = "{estimate}")
```

Table 2.6.: Birthweight model - stratified betas

Parameter	Estimate
sex (female)	-2141.67
sex (male)	-1268.67
$sex (female) \times age$	130.40
$sex (male) \times age$	111.98

Table 2.6.: Birthweight model - stratified betas

Parameter	Estimate

#### 2.2.5. Curved-line regression

If we transform some of our covariates (Xs) and plot the resulting model on the original covariate scale, we end up with curved regression lines:

```
bw_lm3 = lm(weight ~ sex:log(age) - 1, data = bw)
library(palmerpenguins)
ggpenguins <-
  palmerpenguins::penguins |>
  dplyr::filter(species == "Adelie") |>
  ggplot(
    aes(x = bill_length_mm , y = body_mass_g)) +
  geom_point() +
 xlab("Bill length (mm)") +
  ylab("Body mass (g)")
ggpenguins2 = ggpenguins +
  stat_smooth(
   method = "lm",
              formula = y \sim log(x),
              geom = "smooth") +
  xlab("Bill length (mm)") +
  ylab("Body mass (g)")
ggpenguins2 |> print()
```

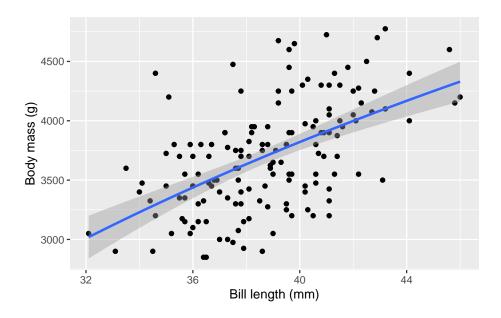


Figure 2.4.: palmerpenguins model with bill\_length entering on log scale

# 2.3. Estimating Linear Models via Maximum Likelihood

## 2.3.1. Likelihood, log-likelihood, and score functions for linear regression

In EPI 203 and [intro-MLEs.qmd#sec-intro-MLEs], we learned how to fit outcome-only models of the form  $p(X=x|\theta)$  to iid data  $\mathbf{x}=(x_1,...,x_n)$  using maximum likelihood estimation.

Now, we apply the same procedure to linear regression models:

$$\mathcal{L}(\tilde{y}|\mathbf{x}, \beta, \sigma^2) = \prod_{i=1}^{n} (2\pi\sigma^2)^{-1/2} \exp\left\{-\frac{1}{2\sigma^2} (y_i - \tilde{x_i}'\beta)^2\right\}$$
(2.4)

$$\ell(\tilde{y}|\mathbf{x},\beta,\sigma^2) = -\frac{n}{2}\log\left\{\sigma^2\right\} - \frac{1}{2\sigma^2}\sum_{i=1}^{n}(y_i - \tilde{x_i}'\beta)^2 \tag{2.5}$$

$$\ell_{\beta}'(\tilde{y}|\mathbf{x},\beta,\sigma^{2}) = -\frac{1}{2\sigma^{2}}\frac{d}{d\beta}\left(\sum_{i=1}^{n}(y_{i} - \tilde{x_{i}}'\beta)^{2}\right) \tag{2.6}$$

#### 2.3.2. Some tools from vector calculus

A few tools from linear algebra will make this analysis go easier (see Fieller (2016), Section 7.2 for details).

$$f_{\beta}(\mathbf{x}) = (f_{\beta}(x_1), f_{\beta}(x_2), ..., f_{\beta}(x_n))^{\top}$$

Let **x** and  $\beta$  be vectors of length p, or in other words, matrices of length  $p \times 1$ :

$$x = \begin{bmatrix} x_1 \\ x_2 \\ \vdots \\ x_p \end{bmatrix} \beta = \begin{bmatrix} \beta_1 \\ \beta_2 \\ \vdots \\ \beta_p \end{bmatrix}$$

Then

$$x'\equiv x^{\top}\equiv [x_1,x_2,...,x_p]$$

and

$$x'\beta = [x_1, x_2, ..., x_p] \begin{bmatrix} \beta_1 \\ \beta_2 \\ \vdots \\ \beta_p \end{bmatrix} = x_1\beta_1 + x_2\beta_2 + ... + x_p\beta_p$$

If  $f(\beta)$  is a function that takes  $\beta$  as input and outputs a scalar, such as  $f(\beta) = x'\beta$ , then:

$$\frac{d}{d\beta}f(\beta) = \begin{bmatrix} \frac{d}{d\beta_1}f(\beta) \\ \frac{d}{d\beta_2}f(\beta) \\ \vdots \\ \frac{d}{d\beta_p}f(\beta) \end{bmatrix}$$

In particular, if  $f(\beta) = x'\beta$ , then:

$$\frac{d}{d\beta}x'\beta = \begin{bmatrix} \frac{d}{d\beta_1}(x_1\beta_1 + x_2\beta_2 + \dots + x_p\beta_p) \\ \frac{d}{d\beta_2}(x_1\beta_1 + x_2\beta_2 + \dots + x_p\beta_p) \\ \vdots \\ \frac{d}{d\beta_p}(x_1\beta_1 + x_2\beta_2 + \dots + x_p\beta_p) \end{bmatrix} = \begin{bmatrix} x_1 \\ x_2 \\ \vdots \\ x_p \end{bmatrix} = \mathbf{x}$$

In general:

$$\frac{d}{d\beta}x'\beta = x$$

This looks a lot like non-vector calculus, except that you have to transpose the coefficient.

Similarly,

$$\frac{d}{d\beta}\beta'\beta = 2\beta$$

This is like taking the derivative of  $x^2$ .

And finally, if S is a  $p \times p$  matrix, then:

$$\frac{d}{d\beta}\beta'S\beta = 2S\beta$$

Again, this is like taking the derivative of  $cx^2$  with respect to x in non-vector calculus.

Thus:

$$\sum_{i=1}^n (y_i - f_{\beta}(x_i))^2 = (\mathbf{y} - X\beta)'(\mathbf{y} - X\beta)$$

$$(\mathbf{y}-X\beta)'=(\mathbf{y}'-(X\beta)')=(\mathbf{y}'-\beta'X')$$

So

$$\begin{split} (\mathbf{y} - X\beta)'(\mathbf{y} - X\beta) &= (\mathbf{y}' - \beta'X')(\mathbf{y} - X\beta) \\ &= y'y - \beta'X'y - y'X\beta + \beta'X'X\beta \\ &= y'y - 2y'X\beta + \beta'X'X\beta \end{split}$$

#### 2.3.3. Analyzing the linear regression score function

$$\begin{split} \frac{d}{d\beta} \left( \sum_{i=1}^n (y_i - x_i'\beta)^2 \right) &= \frac{d}{d\beta} (\mathbf{y} - X\beta)' (\mathbf{y} - X\beta) \\ &= \frac{d}{d\beta} (y'y - 2y'X\beta + \beta'X'X\beta) \\ &= (-2X'y + 2X'X\beta) \end{split}$$

So if  $\ell(\beta, \sigma^2) = 0$ , then

$$0 = (-2X'y + 2X'X\beta)$$
 
$$2X'y = 2X'X\beta$$
 
$$X'y = X'X\beta$$
 
$$(X'X)^{-1}X'y = \beta$$

The second derivative matrix  $\ell''_{\beta,\beta'}(\beta,\sigma^2;\mathbf{X},\mathbf{y})$  is negative definite at  $\beta=(X'X)^{-1}X'y$ , so  $\hat{\beta}_{ML}=(X'X)^{-1}X'y$  is the MLE for  $\beta$ .

Similarly (not shown):

$$\hat{\sigma}_{ML}^2 = \frac{1}{n} (Y - X \hat{\beta})' (Y - X \hat{\beta})$$

And

$$\begin{split} \mathcal{I}_{\beta} &= E[-\ell_{\beta,\beta'}'(Y|X,\beta,\sigma^2)] \\ &= \frac{1}{\sigma^2} X' X \end{split}$$

So:

$$Var(\hat{\beta}) \approx (\mathcal{I}_{\beta})^{-1} = \sigma^2 (X'X)^{-1}$$

and

$$\hat{\beta}\dot{\sim}N(\beta,\mathcal{I}_{\beta}^{-1})$$

These are all results you have hopefully seen before.

In the Gaussian linear regression case, we also have exact results:

$$\frac{\hat{\beta}_j}{\hat{\mathrm{se}}\left(\hat{\beta}_j\right)} \; \sim \; t_{n-p}$$

In our model 2 above,  $\hat{\mathcal{I}}(\beta)$  is:

bw\_lm2 |> parameters() |> print\_md()

```
bw_lm2 |> vcov()
#>
                (Intercept)
                              sexmale
                                           age sexmale:age
#> (Intercept)
                    1353968 -1353968 -34871.0
                                                    34871.0
#> sexmale
                                                   -67211.0
                   -1353968
                              2596387
                                       34871.0
#> age
                     -34871
                                         899.9
                                                     -899.9
                                34871
#> sexmale:age
                      34871
                               -67211
                                        -899.9
                                                     1743.5
```

If we take the square roots of the diagonals, we get the standard errors listed in the model output:

```
bw_lm2 |> vcov() |> diag() |> sqrt()
#> (Intercept) sexmale age sexmale:age
#> 1163.60 1611.33 30.00 41.76
```

Table 2.7.: Estimated model for birthweight data with interaction term

Parameter	Coefficient	SE	95% CI	t(20)	p
(Intercept)	-2141.67	1163.60	(-4568.90, 285.56)	-1.84	0.081
sex (male)	872.99	1611.33	(-2488.18, 4234.17)	0.54	0.594
age	130.40	30.00	(67.82, 192.98)	4.35	< .001
$\begin{array}{l} \text{sex (male)} \times \\ \text{age} \end{array}$	-18.42	41.76	(-105.52, 68.68)	-0.44	0.664

So we can do confidence intervals, hypothesis tests, and p-values exactly as in the one-variable case we looked at previously.

#### 2.3.4. Residual Standard Deviation

 $\hat{\sigma}$  represents an *estimate* of the *Residual Standard Deviation* parameter,  $\sigma$ . We can extract  $\hat{\sigma}$  from the fitted model, using the sigma() function:

```
sigma(bw_lm2)
#> [1] 180.61347
```

#### 2.3.4.1. $\sigma$ is NOT "Residual standard error"

In the summary.lm() output, this estimate is labeled as "Residual standard error":

```
summary(bw_lm2)
#>
#> Call:
#> lm(formula = weight ~ sex + age + sex:age, data = bw)
#> Residuals:
       Min
                 1Q
                      Median
                                   3Q
                                           Max
#> -246.690 -138.113 -39.129 176.567
                                       274.276
#>
#> Coefficients:
#>
               Estimate Std. Error t value Pr(>|t|)
#> (Intercept) -2141.667
                        1163.601 -1.8405 0.0805744 .
#> sexmale
                872.994
                          1611.331 0.5418 0.5939521
                            29.998 4.3469 0.0003127 ***
#> age
                130.400
#> sexmale:age
                -18.417
                            41.756 -0.4411 0.6638934
#> Signif. codes: 0 '***' 0.001 '**' 0.05 '.' 0.1 ' ' 1
```

```
#>
#> Residual standard error: 180.61 on 20 degrees of freedom
#> Multiple R-squared: 0.64346, Adjusted R-squared: 0.58998
#> F-statistic: 12.032 on 3 and 20 DF, p-value: 0.00010096
```

However, this is a misnomer:

```
library(printr) # captures ? documentation
?stats::sigma
#> Extract Residual Standard Deviation 'Sigma'
#>
#> Description:
#>
#>
        Extract the estimated standard deviation of the errors, the
#>
        "residual standard deviation" (misnamed also "residual standard
        error", e.g., in 'summary.lm()''s output, from a fitted model).
#>
#>
#>
        Many classical statistical models have a _scale parameter_,
#>
        typically the standard deviation of a zero-mean normal (or
        Gaussian) random variable which is denoted as sigma. 'sigma(.)'
#>
#>
        extracts the _estimated_ parameter from a fitted model, i.e.,
#>
        sigma^.
#>
#> Note:
#>
#>
        The misnomer "Residual standard *error*" has been part of too many
        R (and S) outputs to be easily changed there.
#>
```

## 2.4. Inference about Gaussian Linear Regression Models

## 2.4.1. Motivating example: birthweight data

Research question: is there really an interaction between sex and age?

$$\begin{split} &H_0: \beta_{AM} = 0 \\ &H_A: \beta_{AM} \neq 0 \\ &P(|\hat{\beta}_{AM}| > |-18.41724138| \mid H_0) = ? \end{split}$$

#### 2.4.2. Wald tests and CIs

R can give you Wald tests for single coefficients and corresponding CIs:

```
bw_lm2 |>
  parameters() |>
  print_md(
   include_reference = TRUE)
```

Parameter	Coefficient	SE	95% CI	t(20)	p
(Intercept)	-2141.67	1163.60	(-4568.90, 285.56)	-1.84	0.081
sex (female)	0.00		,		
sex (male)	872.99	1611.33	(-2488.18, 4234.17)	0.54	0.594
age	130.40	30.00	(67.82, 192.98)	4.35	< .001
$\begin{array}{l} \text{sex (male)} \times \\ \text{age} \end{array}$	-18.42	41.76	(-105.52, 68.68)	-0.44	0.664

To understand what's happening, let's replicate these results by hand for the interaction term.

#### 2.4.3. P-values

```
bw_lm2 |>
  parameters(keep = "sexmale:age") |>
  print_md(
   include_reference = TRUE)
```

Parameter	Coefficient	SE	95% CI	t(20)	p
$sex (male) \times$	-18.42	41.76	(-105.52, 68.68)	-0.44	0.664
age					

```
beta_hat = coef(summary(bw_lm2))["sexmale:age", "Estimate"]
se_hat = coef(summary(bw_lm2))["sexmale:age", "Std. Error"]
dfresid = bw_lm2$df.residual
t_stat = abs(beta_hat)/se_hat
pval_t =
   pt(-t_stat, df = dfresid, lower.tail = TRUE) +
   pt(t_stat, df = dfresid, lower.tail = FALSE)
```

$$\begin{split} &P\left(|\hat{\beta}_{AM}|>|-18.41724138|\Big|H_0\right)\\ &=\Pr\left(\left|\frac{\hat{\beta}_{AM}}{\hat{SE}(\hat{\beta}_{AM})}\right|>\left|\frac{-18.41724138}{41.75581745}\right|\Big|H_0\right)\\ &=\Pr\left(|T_{20}|>0.44107007|H_0\right)\\ &=0.66389342 \end{split}$$

This matches the result in the table above.

#### 2.4.4. Confidence intervals

```
bw_lm2 |>
  parameters(keep = "sexmale:age") |>
  print_md(
   include_reference = TRUE)
```

Parameter	Coefficient	SE	95% CI	t(20)	p
sex (male) ×	-18.42	41.76	(-105.52, 68.68)	-0.44	0.664
age					

```
q_t = qt(
    p = 0.975,
    df = dfresid,
    lower.tail = TRUE)

q_t = qt(
    p = 0.025,
    df = dfresid,
    lower.tail = TRUE)

confint_radius_t = se_hat * q_t

confint_t = beta_hat + c(-1,1) * confint_radius_t

print(confint_t)

#> [1] 68.68 -105.52
```

This also matches.

### 2.4.5. Gaussian approximations

Here are the asymptotic (Gaussian approximation) equivalents:

#### 2.4.6. P-values

```
bw_lm2 |>
  parameters(keep = "sexmale:age") |>
  print_md(
   include_reference = TRUE)
```

Parameter	Coefficient	SE	95% CI	t(20)	p
$sex (male) \times$	-18.42	41.76	(-105.52, 68.68)	-0.44	0.664
age					

```
pval_z = pnorm(abs(t_stat), lower = FALSE) * 2
print(pval_z)
#> [1] 0.65916227
```

#### 2.4.7. Confidence intervals

```
bw_lm2 |>
  parameters(keep = "sexmale:age") |>
  print_md(
   include_reference = TRUE)
```

Parameter	Coefficient	SE	95% CI	t(20)	p
sex (male) ×	-18.42	41.76	(-105.52, 68.68)	-0.44	0.664
age					

```
confint_radius_z = se_hat * qnorm(0.975, lower = TRUE)
confint_z =
  beta_hat + c(-1,1) * confint_radius_z
print(confint_z)
#> [1] -100.257140 63.422657
```

#### 2.4.8. Likelihood ratio statistics

```
logLik(bw_lm2)
#> 'log Lik.' -156.57929 (df=5)
logLik(bw_lm1)
#> 'log Lik.' -156.69545 (df=4)

llR = (logLik(bw_lm2) - logLik(bw_lm1)) |> as.numeric()
delta_df = (bw_lm1$df.residual - df.residual(bw_lm2))

x_max = 1
```

```
d_lLR = function(x, df = delta_df) dchisq(x, df = df)

chisq_plot =
    ggplot() +
```

```
geom_function(fun = d_1LR) +
stat_function( fun = d_1LR, xlim = c(1LR, x_max), geom = "area", fill = "gray") +
geom_segment(aes(x = 1LR, xend = 1LR, y = 0, yend = d_1LR(1LR)), col = "red") +
xlim(0.0001,x_max) +
ylim(0,4) +
ylab("p(X=x)") +
xlab("log(likelihood ratio) statistic [x]") +
theme_classic()
chisq_plot |> print()
```



Figure 2.5.: Chi-square distribution

Now we can get the p-value:

```
pchisq(
    q = 2*1LR,
    df = delta_df,
    lower = FALSE) |>
    print()
#> [1] 0.6298
```

In practice you don't have to do this by hand; there are functions to do it for you:

```
# built in
library(lmtest)
lrtest(bw_lm2, bw_lm1)
```

#Df	LogLik	Df	Chisq	Pr(>Chisq)
5	-156.57929	NA	NA	NA
4	-156.69545	-1	0.23232327	0.62980648

## 2.5. Goodness of fit

#### 2.5.1. AIC and BIC

When we use likelihood ratio tests, we are comparing how well different models fit the data.

Likelihood ratio tests require "nested" models: one must be a special case of the other.

If we have non-nested models, we can instead use the Akaike Information Criterion (AIC) or Bayesian Information Criterion (BIC):

- AIC =  $-2 * \ell(\hat{\theta}) + 2 * p$
- BIC =  $-2 * \ell(\hat{\theta}) + p * \log(n)$

where  $\ell$  is the log-likelihood of the data evaluated using the parameter estimates  $\hat{\theta}$ , p is the number of estimated parameters in the model (including  $\hat{\sigma}^2$ ), and n is the number of observations.

You can calculate these criteria using the logLik() function, or use the built-in R functions:

#### 2.5.1.1. AIC in R

```
-2 * logLik(bw_lm2) |> as.numeric() +
    2*(length(coef(bw_lm2))+1) # sigma counts as a parameter here
#> [1] 323.15858

AIC(bw_lm2)
#> [1] 323.15858
```

#### 2.5.1.2. BIC in R

```
-2 * logLik(bw_lm2) |> as.numeric() +
   (length(coef(bw_lm2))+1) * log(nobs(bw_lm2))
#> [1] 329.04884

BIC(bw_lm2)
#> [1] 329.04884
```

Large values of AIC and BIC are worse than small values. There are no hypothesis tests or p-values associated with these criteria.

## 2.5.2. (Residual) Deviance

Let q be the number of distinct covariate combinations in a data set.

```
bw.X.unique =
bw |>
count(sex, age)

n_unique.bw = nrow(bw.X.unique)
```

For example, in the birthweight data, there are q=12 unique patterns:

```
bw.X.unique |>
  pander(
    row.names = rownames(bw.X.unique))
```

Table 2.14.: Unique covariate combinations in the birthweight data, with replicate counts

	sex	age	n
1	female	36	2
2	female	37	1
3	female	38	2
4	female	39	2
5	female	40	4
6	female	42	1
7	male	35	1
8	$_{\mathrm{male}}$	36	1

Table 2.14.: Unique covariate combinations in the birthweight data, with replicate counts

	sex	age	n
9	male	37	2
10	$_{\mathrm{male}}$	38	3
11	$_{\mathrm{male}}$	40	4
12	male	41	1

## Note

If a given covariate pattern has more than one observation in a dataset, those observations are called **replicates**.

Then the most complicated model we could fit would have one parameter (a mean) for each of these combinations, plus a variance parameter:

```
lm_max =
  bw |>
  mutate(age = factor(age)) |>
  lm(
    formula = weight ~ sex:age - 1,
    data = _)

lm_max |>
  parameters() |>
  print_md()
```

Table 2.15.: Saturated model for the birthweight data

Parameter	Coefficient	SE	95% CI	t(12)	p
sex (male) ×	2925.00	187.92	(2515.55,	15.56	<
age35			3334.45)		.001
sex (female) $\times$	2570.50	132.88	(2280.98,	19.34	<
age36			2860.02)		.001
$sex (male) \times$	2625.00	187.92	(2215.55,	13.97	<
age36			3034.45)		.001
sex (female) $\times$	2539.00	187.92	(2129.55,	13.51	<
age37			2948.45)		.001
sex (male) $\times$	2737.50	132.88	(2447.98,	20.60	<
age37			3027.02)		.001
sex (female) $\times$	2872.50	132.88	(2582.98,	21.62	<
age38			3162.02)		.001
$sex (male) \times$	2982.00	108.50	(2745.60,	27.48	<
age38			3218.40)		.001
sex (female) $\times$	2846.00	132.88	(2556.48,	21.42	<
age39			3135.52)		.001
sex (female) $\times$	3152.25	93.96	(2947.52,	33.55	<
age40			3356.98)		.001
$sex (male) \times$	3256.25	93.96	(3051.52,	34.66	<
age40			3460.98)		.001
$sex (male) \times$	3292.00	187.92	(2882.55,	17.52	<
age41			3701.45)		.001
sex (female) $\times$	3210.00	187.92	(2800.55,	17.08	<
age42			3619.45)		.001

We call this model the **full**, **maximal**, or **saturated** model for this dataset.

We can calculate the log-likelihood of this model as usual:

```
logLik(lm_max)
#> 'log Lik.' -151.4016 (df=13)
```

We can compare this model to our other models using chi-square tests, as usual:

#### lrtest(lm\_max, bw\_lm2)

#Df	LogLik	Df	Chisq	Pr(>Chisq)
13	-151.40160	NA	NA	NA
5	-156.57929	-8	10.355374	0.24096372

The likelihood ratio statistic for this test is

$$\lambda = 2 * (\ell_{\text{full}} - \ell) = 10.35537421$$

where:

- $\ell_{\rm max}$  is the log-likelihood of the full model: -151.40160056
- $\ell$  is the log-likelihood of our comparison model (two slopes, two intercepts): -156.57928767

This statistic is called the **deviance** or **residual deviance** for our two-slopes and two-intercepts model; it tells us how much the likelihood of that model deviates from the likelihood of the maximal model.

The corresponding p-value tells us whether there we have enough evidence to detect that our two-slopes, two-intercepts model is a worse fit for the data than the maximal model; in other words, it tells us if there's evidence that we missed any important patterns. (Remember, a nonsignificant p-value could mean that we didn't miss anything and a more complicated model is unnecessary, or it could mean we just don't have enough data to tell the difference between these models.)

#### 2.5.3. Null Deviance

Similarly, the least complicated model we could fit would have only one mean parameter, an intercept:

$$\mathrm{E}[Y|X=x] = \beta_0$$

We can fit this model in R like so:

Parameter	Coefficient	SE	95% CI	t(23)	р
(Intercept)	2967.67	57.58	(2848.56, 3086.77)	51.54	< .001

This model also has a likelihood:

```
logLik(lm0)
#> 'log Lik.' -168.95497 (df=2)
```

And we can compare it to more complicated models using a likelihood ratio test:

#Df	LogLik	Df	Chisq	Pr(>Chisq)
5	-156.57929	NA	NA	NA
2	-168.95497	-3	24.751358	1.74e-05

The likelihood ratio statistic for the test comparing the null model to the maximal model is

$$\lambda = 2*(\ell_{\rm full} - \ell_0) = 35.10673188$$

where:

- $\ell_0$  is the log-likelihood of the null model: -168.9549665
- $\ell_{\rm full}$  is the log-likelihood of the maximal model: -151.40160056

In R, this test is:

#### lrtest(lm\_max, lm0)

#Df	LogLik	Df	Chisq	Pr(>Chisq)
13	-151.40160	NA	NA	NA
2	-168.95497	-11	35.106732	0.00023795

This log-likelihood ratio statistic is called the **null deviance**. It tells us whether we have enough data to detect a difference between the null and full models.

## 2.6. Rescaling

### 2.6.1. Rescale age

```
bw =
  bw |>
  mutate(
   `age - mean` = age - mean(age),
```

```
`age - 36wks` = age - 36
)

lm1c = lm(weight ~ sex + `age - 36wks`, data = bw)

lm2c = lm(weight ~ sex + `age - 36wks` + sex:`age - 36wks`, data = bw)

parameters(lm2c, ci_method = "wald") |> print_md()
```

Parameter	Coefficient	SE	95% CI	t(20)	p
$\overline{\text{(Intercept)}}$	2552.73	97.59	(2349.16,	26.16	<
			2756.30)		.001
sex (male)	209.97	129.75	(-60.68,	1.62	0.121
			480.63)		
age - 36wks	130.40	30.00	(67.82, 192.98)	4.35	<
					.001
$sex (male) \times age -$	-18.42	41.76	(-105.52,	-0.44	0.664
36wks			68.68)		

Compare with what we got without rescaling:

```
parameters(bw_lm2, ci_method = "wald") |> print_md()
```

Parameter	Coefficient	SE	95% CI	t(20)	p
(Intercept)	-2141.67	1163.60	(-4568.90, 285.56)	-1.84	0.081
sex (male)	872.99	1611.33	(-2488.18, 4234.17)	0.54	0.594
age	130.40	30.00	(67.82, 192.98)	4.35	< .001

Parameter	Coefficient	SE	95% CI	t(20)	р
$\overline{\text{sex (male)}} \times$	-18.42	41.76	(-105.52, 68.68)	-0.44	0.664
age					

## 2.7. Prediction

#### 2.7.1. Prediction for linear models

**Definition 2.1** (Predicted value). In a regression model p(y|x), the **predicted value** of y given x is the estimated mean of Y given X:

$$\hat{y} \stackrel{\text{def}}{=} \hat{\mathbf{E}} \left[ Y | X = x \right]$$

For linear models, the predicted value can be straightforwardly calculated by multiplying each predictor value  $x_j$  by its corresponding coefficient  $\beta_j$  and adding up the results:

$$\begin{split} \hat{Y} &= \hat{E}[Y|X=x] \\ &= x'\hat{\beta} \\ &= \hat{\beta}_0 \cdot 1 + \hat{\beta}_1 x_1 + \ldots + \hat{\beta}_p x_p \end{split}$$

#### 2.7.2. Example: prediction for the birthweight data

```
X = c(1,1,40)
sum(X * coef(bw_lm1))
#> [1] 3225.4905
```

R has built-in functions for prediction:

If you don't provide newdata, R will use the covariate values from the original dataset:

```
predict(bw_lm1)
#>
                                                     5
                     2
                                3
#> 3225.4905 3062.4512 2983.7019 2578.8739 3225.4905 3062.4512 2621.0189 2820.6626
                    10
                               11
                                         12
                                                    13
#> 2741.9132 3304.2399 2862.8076 2941.5569 3346.3849 3062.4512 3225.4905 2699.7683
          17
                    18
                               19
                                         20
                                                    21
                                                              22
                                                                         23
#> 2862.8076 2578.8739 2983.7019 2820.6626 3225.4905 2941.5569 2983.7019 3062.4512
```

These special predictions are called the *fitted values* of the dataset:

**Definition 2.2.** For a given dataset  $(\tilde{Y}, \tilde{X})$  and corresponding fitted model  $p_{\hat{\beta}}(y|x)$ , the **fitted value** of  $y_i$  is the predicted value of y when  $X = x_i$  using the estimate parameters  $\hat{\beta}$ .

R has an extra function to get these values:

```
fitted(bw_lm1)
#>
           1
                      2
                                3
                                           4
                                                     5
                                                                6
                                                                          7
                                                                                     8
#> 3225.4905 3062.4512 2983.7019 2578.8739 3225.4905 3062.4512 2621.0189 2820.6626
           9
                     10
                               11
                                          12
                                                    13
                                                               14
                                                                         15
#> 2741.9132 3304.2399 2862.8076 2941.5569 3346.3849 3062.4512 3225.4905 2699.7683
#>
                     18
                               19
                                          20
                                                    21
                                                               22
                                                                         23
                                                                                    24
          17
#> 2862.8076 2578.8739 2983.7019 2820.6626 3225.4905 2941.5569 2983.7019 3062.4512
```

# 2.7.3. Quantifying uncertainty in predictions

```
bw_lm1 |>
    predict(
        newdata = x,
        se.fit = TRUE)

#> $fit

#>        1

#> 3225.4905

#>

#> $se.fit

#> [1] 61.459866

#>

#> $df

#> [1] 21

#>

#> $residual.scale

#> [1] 177.11588
```

This is a list(); you can extract the elements with \$ or magrittr::use\_series():

```
bw_lm1 |>
predict(
```

```
newdata = x,
se.fit = TRUE) |>
use_series(se.fit)
#> [1] 61.459866
```

You can get **confidence intervals** for  $\mathbb{E}[Y|X=x]$ :

```
bw_lm1 |> predict(
  newdata = x,
  interval = "confidence")
```

fit	lwr	upr
3225.4905	3097.6778	3353.3033

You can also get **prediction intervals** for the value of an individual outcome Y:

```
bw_lm1 |>
  predict(newdata = x, interval = "predict")
```

fit	lwr	upr
3225.4905	2835.6123	3615.3688

The warning from the last command is: "predictions on current data refer to *future* responses" (since you already know what happened to the current data, and thus don't need to predict it).

See ?predict.lm for more.

# 2.8. Diagnostics

## 2.8.1. Assumptions in linear regression models

$$Y|\tilde{X} \sim N(\tilde{X}'\beta, \sigma^2)$$

- 1. Normality: The distribution conditional on a given X value is normal
- 2. Correct Functional Form: The conditional means have the structure

$$E[Y|\tilde{X} = \tilde{x}] = \tilde{x}'\beta$$

- 3. Homosked asticity: The variance  $\sigma^2$  is constant (with respect to  $\tilde{x}$ )
  - 4. Independence: The observations are statistically independent

#### 2.8.2. Direct visualization

The most direct way to examine the fit of a model is to compare it to the raw observed data.

```
bw =
  bw |>
  mutate(
    predlm2 = predict(bw_lm2)
) |>
  arrange(sex, age)

plot1_interact =
  plot1 %+% bw +
  geom_line(aes(y = predlm2))

print(plot1_interact)
```



Figure 2.6.: Birthweight model with interaction term

It's not easy to assess these assumptions from this model. If there are multiple continuous covariates, it becomes even harder to visualize the raw data.

## 2.8.3. Residuals

Maybe we can transform the data and model in some way to make it easier to inspect.

**Definition 2.3** (Residual noise). The **residual noise** in a probabilistic model p(Y) is the difference between an observed value y and its distributional mean:

$$\epsilon(y) \stackrel{\text{def}}{=} y - \mathbb{E}[Y] \tag{2.7}$$

We use the same notation for residual noise that we used for errors.  $\mathbb{E}[Y]$  can be viewed as an estimate of Y, before y is observed. Conversely, each observation y can be viewed as an estimate of  $\mathbb{E}[Y]$  (albeit an imprecise one, individually, since n = 1).

We can rearrange Equation 2.7 to view y as the sum of its mean plus the residual noise:

$$y = \mathbb{E}\left[Y\right] + \epsilon y$$

**Theorem 2.1** (Residuals in Gaussian models). If Y has a Gaussian distribution, then  $\epsilon Y$  also has a Gaussian distribution, and vice versa.

*Proof.* Left to the reader.  $\Box$ 

**Definition 2.4** (Residual errors of a fitted model value). The **residual** of a fitted value  $\hat{y}$  (shorthand: "residual") is its error:

$$e(\hat{y}) \stackrel{\text{def}}{=} \epsilon(\hat{y})$$
$$= y - \hat{y}$$

 $e(\hat{y})$  can be seen as the maximum likelihood estimate of the residual noise:

$$\begin{split} e(\hat{y}) &= y - \hat{y} \\ &= \hat{\epsilon}_{ML} \end{split}$$

\_\_\_\_

## 2.8.3.1. General characteristics of residuals

**Theorem 2.2.** For unbiased estimators  $\hat{\theta}$ :

$$\mathbb{E}\left[e(y)\right] = 0\tag{2.8}$$

$$Var(e(y)) \approx \sigma^2$$
 (2.9)

Proof.

Equation 2.9:

$$\begin{split} \mathbb{E}\left[e(y)\right] &= \mathbb{E}\left[y - \hat{y}\right] \\ &= \mathbb{E}\left[y\right] - \mathbb{E}\left[\hat{y}\right] \\ &= \mathbb{E}\left[y\right] - \mathbb{E}\left[y\right] \\ &= 0 \end{split}$$

Equation 2.9:

$$\begin{split} \operatorname{Var}\left(e(y)\right) &= \operatorname{Var}\left(y - \hat{y}\right) \\ &= \operatorname{Var}\left(y\right) + \operatorname{Var}\left(\hat{y}\right) - 2\operatorname{Cov}\left(y, \hat{y}\right) \\ &\stackrel{\dot{\approx}}{\approx} \operatorname{Var}\left(y\right) + 0 - 2 \cdot 0 \\ &= \operatorname{Var}\left(y\right) \\ &= \sigma^2 \end{split}$$

## 2.8.3.2. Characteristics of residuals in Gaussian models

With enough data and a correct model, the residuals will be approximately Guassian distributed, with variance  $\sigma^2$ , which we can estimate using  $\hat{\sigma}^2$ : that is:

$$e_i \; \sim_{\mathrm{iid}} \; N(0, \hat{\sigma}^2)$$

**Example 2.1** (residuals in birthweight data). R provides a function for residuals:

res	id(bw_lm2)					
#>	1	2	3	4	5	6
#>	176.266667	-140.733333	-144.133333	-59.533333	177.466667	-126.933333
#>	7	8	9	10	11	12
#>	-68.933333	242.666667	-139.333333	51.666667	156.666667	-125.133333
#>	13	14	15	16	17	18
#>	274.275862	-137.706897	-27.689655	-246.689655	-191.672414	189.327586
#>	19	20	21	22	23	24
#>	-11.672414	-242.637931	-47.637931	262.362069	210.362069	-30.620690

Exercise 2.7. Check R's output by computing the residuals directly.

Solution.

```
bw$weight - fitted(bw_lm2)
#>
                                                               5
                                                                            6
             1
                                      3
#>
    176.266667 -140.733333 -144.133333
                                         -59.533333
                                                      177.466667 -126.933333
             7
                          8
#>
                                                  10
                                                              11
                                                                           12
                                          51.666667 156.666667 -125.133333
    -68.933333 242.666667 -139.333333
```

```
13
                        14
                                    15
                                                16
                            -27.689655 -246.689655 -191.672414
#>
    274.275862 -137.706897
                                                                189.327586
#>
            19
                        20
                                    21
                                                22
                                                            23
                                                                        24
   -11.672414 -242.637931 -47.637931 262.362069 210.362069
                                                                -30.620690
```

This matches R's output!

## 2.8.3.3. Graph the residuals

```
bw = bw |>
 mutate(resids_intxn =
           weight - fitted(bw_lm2))
plot_bw_resid =
  bw |>
  ggplot(aes(
    x = age,
    y = resids_intxn,
    linetype = sex,
    shape = sex,
    col = sex)) +
  theme bw() +
  xlab("Gestational age (weeks)") +
  ylab("residuals (grams)") +
  theme(legend.position = "bottom") +
  \# expand_limits(y = 0, x = 0) +
  geom_point(alpha = .7)
print(plot_bw_resid + facet_wrap(~ sex))
```



Figure 2.7.: Residuals of interaction model for birthweight data

**Definition 2.5** (Standardized residuals).

$$r_i = \frac{e_i}{\widehat{SD}(e_i)}$$

Hence, with enough data and a correct model, the standardized residuals will be approximately standard Gaussian; that is,

$$r_i \sim_{\mathrm{iid}} N(0,1)$$

## 2.8.4. Marginal distributions of residuals

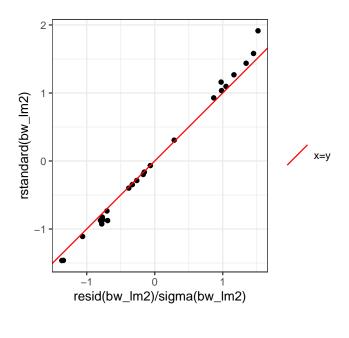
To look for problems with our model, we can check whether the residuals  $e_i$  and standardized residuals  $r_i$  look like they have the distributions that they are supposed to have, according to the model.

#### 2.8.4.1. Standardized residuals in R

```
rstandard(bw lm2)
                             2
#>
                                           3
                                                                        5
#>
    1.159816604
                 -0.926010912 -0.874791659
                                             -0.347225534
                                                             1.035066486 -0.734731462
#>
                             8
                                           9
                                                                       11
                                                                                     12
                                                        10
   -0.399008578
                  1.437516422
                                               0.306064623
                                                             0.928066921
#>
                               -0.825387176
                                                                          -0.876159249
#>
              13
                            14
                                          15
                                                        16
                                                                       17
                                                                                     18
    1.914278022 -0.865592113 -0.164299301 -1.463757406
#>
                                                           -1.110159894
                                                                           1.096578735
#>
              19
                            20
                                          21
                                                        22
                                                                       23
                                                                                     24
   -0.067606211 -1.461586459 -0.286958245
                                               1.580399427
                                                             1.267165237 -0.198054338
resid(bw_lm2)/sigma(bw_lm2)
#>
               1
                                           3
                                                                        5
#>
    0.975933108
                 -0.779196215
                               -0.798020946
                                              -0.329617347
                                                             0.982577131
                                                                          -0.702789954
#>
                             8
                                           9
                                                        10
                                                                       11
                                                                                     12
   -0.381662191
                  1.343569030 -0.771444855
                                               0.286062087
                                                             0.867414071
                                                                          -0.692823920
#>
                            14
              13
#>
                                          15
                                                        16
                                                                       17
                                                                                     18
                                                            -1.061229886
#>
    1.518579205 -0.762439786
                               -0.153308914
                                             -1.365843052
                                                                           1.048247313
                            20
                                          21
                                                        22
                                                                       23
#>
              19
                                                                                     24
   -0.064626485 -1.343409930 -0.263756245
                                              1.452616279
                                                            1.164708630 -0.169537130
```

These are not quite the same, because R is doing something more complicated and precise to get the standard errors. Let's not worry about those details for now; the difference is pretty small in this case:

```
rstandard_compare_plot =
 tibble(
   x = resid(bw_lm2)/sigma(bw_lm2),
   y = rstandard(bw_lm2)) |>
 ggplot(aes(x = x, y = y)) +
 geom_point() +
 theme_bw() +
 coord_equal() +
 xlab("resid(bw_lm2)/sigma(bw_lm2)") +
 ylab("rstandard(bw_lm2)") +
 geom_abline(
   aes(
   intercept = 0,
   slope = 1,
   col = "x=y")) +
 labs(colour="") +
  scale_colour_manual(values="red")
print(rstandard_compare_plot)
```



Let's add these residuals to the tibble of our dataset:

```
bw =
  bw |>
  mutate(
    fitted_lm2 = fitted(bw_lm2),

    resid_lm2 = resid(bw_lm2),
    # resid_lm2 = weight - fitted_lm2,

std_resid_lm2 = resid_lm2 / sigma(bw_lm2),
    # std_resid_lm2 = resid_lm2 / sigma(bw_lm2)
)
```

```
bw |>
  select(
    sex,
    age,
    weight,
    fitted_lm2,
    resid_lm2,
    std_resid_lm2
)
```

sex	age	weight	fitted_lm2	resid_lm2	std_resid_lm2
female	36	2729	2552.7333	176.266667	1.15981660
female	36	2412	2552.7333	-140.733333	-0.92601091
female	37	2539	2683.1333	-144.133333	-0.87479166
female	38	2754	2813.5333	-59.533333	-0.34722553
female	38	2991	2813.5333	177.466667	1.03506649
female	39	2817	2943.9333	-126.933333	-0.73473146
female	39	2875	2943.9333	-68.933333	-0.39900858
female	40	3317	3074.3333	242.666667	1.43751642
female	40	2935	3074.3333	-139.333333	-0.82538718
female	40	3126	3074.3333	51.666667	0.30606462
female	40	3231	3074.3333	156.666667	0.92806692
female	42	3210	3335.1333	-125.133333	-0.87615925
$_{\mathrm{male}}$	35	2925	2650.7241	274.275862	1.91427802
$_{\mathrm{male}}$	36	2625	2762.7069	-137.706897	-0.86559211
$_{\mathrm{male}}$	37	2847	2874.6897	-27.689655	-0.16429930
$_{ m male}$	37	2628	2874.6897	-246.689655	-1.46375741
$_{ m male}$	38	2795	2986.6724	-191.672414	-1.11015989
$_{\mathrm{male}}$	38	3176	2986.6724	189.327586	1.09657874
$_{\mathrm{male}}$	38	2975	2986.6724	-11.672414	-0.06760621
male	40	2968	3210.6379	-242.637931	-1.46158646

2. Linear (Gaussian) Models

sex	age	weight	$fitted\_lm2$	resid_lm2	$std\_resid\_lm2$
male	40	3163	3210.6379	-47.637931	-0.28695825
male	40	3473	3210.6379	262.362069	1.58039943
male	40	3421	3210.6379	210.362069	1.26716524
male	41	3292	3322.6207	-30.620690	-0.19805434

Now let's build histograms:

```
resid_marginal_hist =
  bw |>
  ggplot(aes(x = resid_lm2)) +
  geom_histogram()

print(resid_marginal_hist)
```

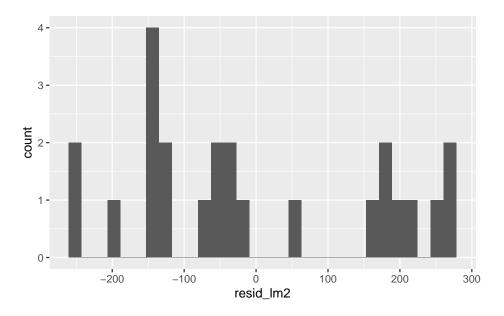


Figure 2.8.: Marginal distribution of (nonstandardized) residuals

Hard to tell with this small amount of data, but I'm a bit concerned that the histogram doesn't show a bell-curve shape.

```
std_resid_marginal_hist =
  bw |>
  ggplot(aes(x = std_resid_lm2)) +
  geom_histogram()

print(std_resid_marginal_hist)
```

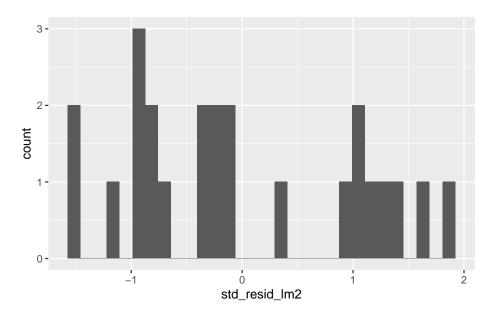


Figure 2.9.: Marginal distribution of standardized residuals

This looks similar, although the scale of the x-axis got narrower, because we divided by  $\hat{\sigma}$  (roughly speaking).

Still hard to tell if the distribution is Gaussian.

# 2.8.5. QQ plot of standardized residuals

Another way to assess normality is the QQ plot of the standardized residuals versus normal quantiles:

```
library(ggfortify)
# needed to make ggplot2::autoplot() work for `lm` objects

qqplot_lm2_auto =
  bw_lm2 |>
  autoplot(
    which = 2, # options are 1:6; can do multiple at once
    ncol = 1) +
  theme_classic()

print(qqplot_lm2_auto)
```



If the Gaussian model were correct, these points should follow the dotted line.

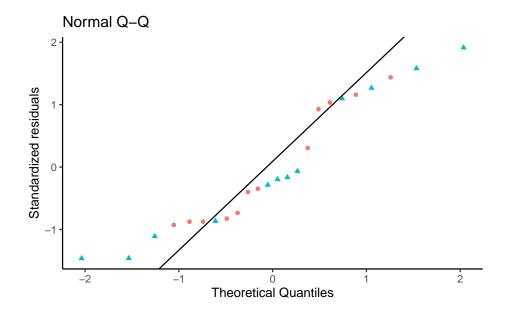
Fig 2.4 panel (c) in Dobson and Barnett (2018) is a little different; they

didn't specify how they produced it, but other statistical analysis systems do things differently from R.

## 2.8.5.1. QQ plot - how it's built

Let's construct it by hand:

```
bw = bw |>
 mutate(
   p = (rank(std_resid_lm2) - 1/2)/n(), # "Blom's method"
    expected_quantiles_lm2 = qnorm(p)
qqplot_lm2 =
  bw |>
  ggplot(
    aes(
     x = expected_quantiles_lm2,
      y = std_resid_lm2,
      col = sex,
      shape = sex)
  ) +
  geom_point() +
  theme_classic() +
 theme(legend.position='none') + # removing the plot legend
  ggtitle("Normal Q-Q") +
  xlab("Theoretical Quantiles") +
 ylab("Standardized residuals")
# find the expected line:
```



#### 2.8.6. Conditional distributions of residuals

If our Gaussian linear regression model is correct, the residuals  $e_i$  and standardized residuals  $r_i$  should have:

- an approximately Gaussian distribution, with:
  - a mean of 0
  - a constant variance

This should be true for every value of x.

If we didn't correctly guess the functional form of linear component of the mean,

$$E[Y|X = x] = \beta_0 + \beta_1 X_1 + ... + \beta_p X_p$$

Then the the residuals might have nonzero mean.

Regardless of whether we guessed the mean function correctly, ther the variance of the residuals might differ between values of x.

#### 2.8.6.1. Residuals versus fitted values

To look for these issues, we can plot the residuals  $e_i$  against the fitted values  $\hat{y}_i$  (Figure 2.10).

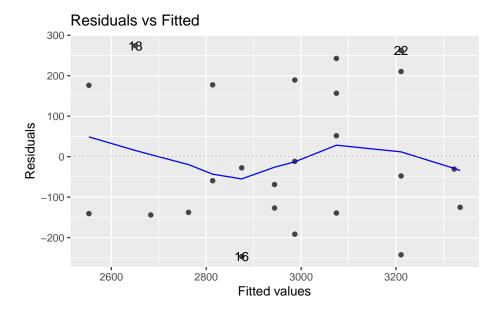


Figure 2.10.: birthweight model (Equation 2.2): residuals versus fitted values

If the model is correct, the blue line should stay flat and close to 0, and the cloud of dots should have the same vertical spread regardless of the fitted value.

If not, we probably need to change the functional form of linear component of the mean,

$$\mathrm{E}[Y|X=x] = \beta_0 + \beta_1 X_1 + \ldots + \beta_p X_p$$

## 2.8.6.2. Scale-location plot

We can also plot the square roots of the absolute values of the standardized residuals against the fitted values (Figure 2.11).

autoplot(bw\_lm2, which = 3, ncol = 1) |> print()

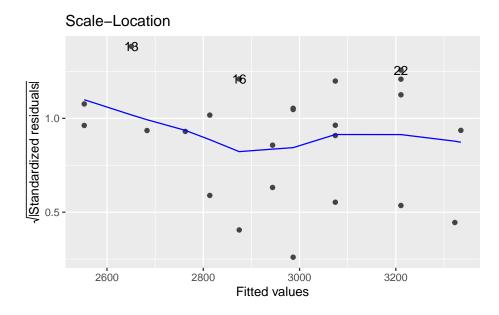


Figure 2.11.: Scale-location plot of birthweight data

Here, the blue line doesn't need to be near 0, but it should be flat. If not, the residual variance  $\sigma^2$  might not be constant, and we might need to transform our outcome Y (or use a model that allows non-constant variance).

## 2.8.6.3. Residuals versus leverage

We can also plot our standardized residuals against "leverage", which roughly speaking is a measure of how unusual each  $x_i$  value is. Very unusual  $x_i$  values can have extreme effects on the model fit, so we might want to remove those observations as outliers, particularly if they have large residuals.



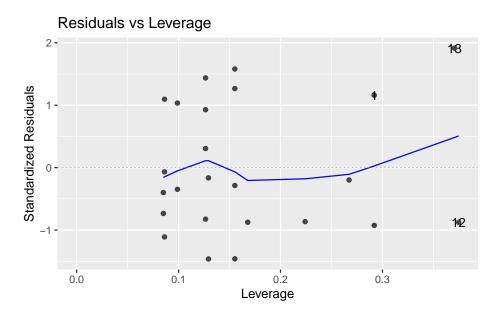


Figure 2.12.: birthweight model with interactions (Equation 2.2): residuals versus leverage

The blue line should be relatively flat and close to 0 here.

## 2.8.7. Diagnostics constructed by hand

```
bw =
  bw |>
  mutate(
    predlm2 = predict(bw_lm2),
    residlm2 = weight - predlm2,
    std_resid = residlm2 / sigma(bw_lm2),
    # std_resid_builtin = rstandard(bw_lm2), # uses leverage
    sqrt_abs_std_resid = std_resid |> abs() |> sqrt()
)
```

#### Residuals vs fitted

```
resid_vs_fit = bw |>
    ggplot(
       aes(x = predlm2, y = residlm2, col = sex, shape = sex)
) +
    geom_point() +
    theme_classic() +
    geom_hline(yintercept = 0)
```

```
print(resid_vs_fit)
```



## Standardized residuals vs fitted

```
bw |>
  ggplot(
   aes(x = predlm2, y = std_resid, col = sex, shape = sex)
) +
  geom_point() +
  theme_classic() +
  geom_hline(yintercept = 0)
```



## Standardized residuals vs gestational age

```
bw |>
  ggplot(
   aes(x = age, y = std_resid, col = sex, shape = sex)
) +
  geom_point() +
  theme_classic() +
  geom_hline(yintercept = 0)
```



## sqrt(abs(rstandard())) vs fitted

Compare with autoplot(bw\_lm2, 3)

```
bw |>
    ggplot(
    aes(x = predlm2, y = sqrt_abs_std_resid, col = sex, shape = sex)
) +
    geom_point() +
    theme_classic() +
    geom_hline(yintercept = 0)
```



# 2.9. Model selection

If we have a lot of covariates in our dataset, we might want to choose a small subset to use in our model.

There are a few possible metrics to consider for choosing a "best" model.

## 2.9.1. Mean squared error

We might want to minimize the **mean squared error**,  $\mathrm{E}[(y-\hat{y})^2]$ , for new observations that weren't in our data set when we fit the model.

Unfortunately,

$$\frac{1}{n}\sum_{i=1}^n(y_i-\hat{y}_i)^2$$

gives a biased estimate of  $\mathrm{E}[(y-\hat{y})^2]$  for new data. If we want an unbiased estimate, we will have to be clever.

#### 2.9.2. Cross-validation

```
data("carbohydrate", package = "dobson")
library(cvTools)
full.model <- lm(carbohydrate ~ ., data = carbohydrate)
temp =
   cvFit(full.model, data = carbohydrate, K = 5, R = 10,
y = carbohydrate$carbohydrate)</pre>
```

# 2.10. Categorical covariates with more than two levels

## 2.10.1. Example: birthweight

In the birthweight example, the variable sex had only two observed values:

```
unique(bw$sex)
#> [1] female male
#> Levels: female male
```

If there are more than two observed values, we can't just use a single variable with 0s and 1s.

# 2.10.2.

For example, Table 2.25 shows the (in)famous  $^4$  iris data (Anderson (1935)), and Table 2.26 provides summary statistics. The data include three species: "setosa", "versicolor", and "virginica".

## iris

Table 2.25.: The iris data

	Table 2.	20 1110 1113 (	iata	
Sepal.Length	Sepal.Width	Petal.Length	Petal.Width	Species
5.1	3.5	1.4	0.2	setosa
4.9	3.0	1.4	0.2	setosa
4.7	3.2	1.3	0.2	setosa
4.6	3.1	1.5	0.2	setosa
5.0	3.6	1.4	0.2	setosa
5.4	3.9	1.7	0.4	setosa
4.6	3.4	1.4	0.3	setosa
5.0	3.4	1.5	0.2	setosa
4.4	2.9	1.4	0.2	setosa
4.9	3.1	1.5	0.1	setosa
5.4	3.7	1.5	0.2	setosa
4.8	3.4	1.6	0.2	setosa
4.8	3.0	1.4	0.1	setosa
4.3	3.0	1.1	0.1	setosa
5.8	4.0	1.2	0.2	setosa
5.7	4.4	1.5	0.4	setosa
5.4	3.9	1.3	0.4	setosa
5.1	3.5	1.4	0.3	setosa
5.7	3.8	1.7	0.3	setosa
5.1	3.8	1.5	0.3	setosa

<sup>&</sup>lt;sup>4</sup>https://www.meganstodel.com/posts/no-to-iris/

Table 2.25.: The iris data

	Table 2.25.: The iris data				
Sepal.Length	Sepal.Width	Petal.Length	Petal.Width	Species	
5.4	3.4	1.7	0.2	setosa	
5.1	3.7	1.5	0.4	setosa	
4.6	3.6	1.0	0.2	setosa	
5.1	3.3	1.7	0.5	setosa	
4.8	3.4	1.9	0.2	setosa	
5.0	3.0	1.6	0.2	setosa	
5.0	3.4	1.6	0.4	setosa	
5.2	3.5	1.5	0.2	setosa	
5.2	3.4	1.4	0.2	setosa	
4.7	3.2	1.6	0.2	setosa	
4.8	3.1	1.6	0.2	setosa	
5.4	3.4	1.5	0.4	setosa	
5.2	4.1	1.5	0.1	setosa	
5.5	4.2	1.4	0.2	setosa	
4.9	3.1	1.5	0.2	setosa	
5.0	3.2	1.2	0.2	setosa	
5.5	3.5	1.3	0.2	setosa	
4.9	3.6	1.4	0.1	setosa	
4.4	3.0	1.3	0.2	setosa	
5.1	3.4	1.5	0.2	setosa	
5.0	3.5	1.3	0.3	setosa	
4.5	2.3	1.3	0.3	setosa	
4.4	3.2	1.3	0.2	setosa	
5.0	3.5	1.6	0.6	setosa	
5.1	3.8	1.9	0.4	setosa	
4.8	3.0	1.4	0.3	setosa	
5.1	3.8	1.6	0.2	setosa	
4.6	3.2	1.4	0.2	setosa	
5.3	3.7	1.5	0.2	setosa	
5.0	3.3	1.4	0.2	setosa	

Table 2.25.: The iris data

Sepal.Length	Sepal.Width	Petal.Length	Petal.Width	Species
7.0	3.2	4.7	1.4	versicolor
6.4	3.2	4.5	1.5	versicolor
6.9	3.1	4.9	1.5	versicolor
5.5	2.3	4.0	1.3	versicolor
6.5	2.8	4.6	1.5	versicolor
5.7	2.8	4.5	1.3	versicolor
6.3	3.3	4.7	1.6	versicolor
4.9	2.4	3.3	1.0	versicolor
6.6	2.9	4.6	1.3	versicolor
5.2	2.7	3.9	1.4	versicolor
5.0	2.0	3.5	1.0	versicolor
5.9	3.0	4.2	1.5	versicolor
6.0	2.2	4.0	1.0	versicolor
6.1	2.9	4.7	1.4	versicolor
5.6	2.9	3.6	1.3	versicolor
6.7	3.1	4.4	1.4	versicolor
5.6	3.0	4.5	1.5	versicolor
5.8	2.7	4.1	1.0	versicolor
6.2	2.2	4.5	1.5	versicolor
5.6	2.5	3.9	1.1	versicolor
5.9	3.2	4.8	1.8	versicolor
6.1	2.8	4.0	1.3	versicolor
6.3	2.5	4.9	1.5	versicolor
6.1	2.8	4.7	1.2	versicolor
6.4	2.9	4.3	1.3	versicolor
6.6	3.0	4.4	1.4	versicolor
6.8	2.8	4.8	1.4	versicolor
6.7	3.0	5.0	1.7	versicolor
6.0	2.9	4.5	1.5	versicolor
5.7	2.6	3.5	1.0	versicolor

Table 2.25.: The iris data

Sepal.Length	Sepal.Width	Petal.Length	Petal.Width	Species
5.5	2.4	3.8	1.1	versicolor
5.5	2.4	3.7	1.0	versicolor
5.8	2.7	3.9	1.2	versicolor
6.0	2.7	5.1	1.6	versicolor
5.4	3.0	4.5	1.5	versicolor
6.0	3.4	4.5	1.6	versicolor
6.7	3.1	4.7	1.5	versicolor
6.3	2.3	4.4	1.3	versicolor
5.6	3.0	4.1	1.3	versicolor
5.5	2.5	4.0	1.3	versicolor
5.5	2.6	4.4	1.2	versicolor
6.1	3.0	4.6	1.4	versicolor
5.8	2.6	4.0	1.2	versicolor
5.0	2.3	3.3	1.0	versicolor
5.6	2.7	4.2	1.3	versicolor
5.7	3.0	4.2	1.2	versicolor
5.7	2.9	4.2	1.3	versicolor
6.2	2.9	4.3	1.3	versicolor
5.1	2.5	3.0	1.1	versicolor
5.7	2.8	4.1	1.3	versicolor
6.3	3.3	6.0	2.5	virginica
5.8	2.7	5.1	1.9	virginica
7.1	3.0	5.9	2.1	virginica
6.3	2.9	5.6	1.8	virginica
6.5	3.0	5.8	2.2	virginica
7.6	3.0	6.6	2.1	virginica
4.9	2.5	4.5	1.7	virginica
7.3	2.9	6.3	1.8	virginica
6.7	2.5	5.8	1.8	virginica
7.2	3.6	6.1	2.5	virginica

Table 2.25.: The iris data

	Table 2.25.: The iris data				
Sepal.Length	Sepal.Width	Petal.Length	Petal.Width	Species	
6.5	3.2	5.1	2.0	virginica	
6.4	2.7	5.3	1.9	virginica	
6.8	3.0	5.5	2.1	virginica	
5.7	2.5	5.0	2.0	virginica	
5.8	2.8	5.1	2.4	virginica	
6.4	3.2	5.3	2.3	virginica	
6.5	3.0	5.5	1.8	virginica	
7.7	3.8	6.7	2.2	virginica	
7.7	2.6	6.9	2.3	virginica	
6.0	2.2	5.0	1.5	virginica	
6.9	3.2	5.7	2.3	virginica	
5.6	2.8	4.9	2.0	virginica	
7.7	2.8	6.7	2.0	virginica	
6.3	2.7	4.9	1.8	virginica	
6.7	3.3	5.7	2.1	virginica	
7.2	3.2	6.0	1.8	virginica	
6.2	2.8	4.8	1.8	virginica	
6.1	3.0	4.9	1.8	virginica	
6.4	2.8	5.6	2.1	virginica	
7.2	3.0	5.8	1.6	virginica	
7.4	2.8	6.1	1.9	virginica	
7.9	3.8	6.4	2.0	virginica	
6.4	2.8	5.6	2.2	virginica	
6.3	2.8	5.1	1.5	virginica	
6.1	2.6	5.6	1.4	virginica	
7.7	3.0	6.1	2.3	virginica	
6.3	3.4	5.6	2.4	virginica	
6.4	3.1	5.5	1.8	virginica	
6.0	3.0	4.8	1.8	virginica	
6.9	3.1	5.4	2.1	virginica	

Table 2.25.: The iris data

Sepal.Length	Sepal.Width	Petal.Length	Petal.Width	Species
6.7	3.1	5.6	2.4	virginica
6.9	3.1	5.1	2.3	virginica
5.8	2.7	5.1	1.9	virginica
6.8	3.2	5.9	2.3	virginica
6.7	3.3	5.7	2.5	virginica
6.7	3.0	5.2	2.3	virginica
6.3	2.5	5.0	1.9	virginica
6.5	3.0	5.2	2.0	virginica
6.2	3.4	5.4	2.3	virginica
5.9	3.0	5.1	1.8	virginica

```
library(table1)
table1(
  x = ~ . | Species,
  data = iris,
  overall = FALSE
)
```

If we want to model Sepal.Length by species, we could create a variable X that represents "setosa" as X=1, "virginica" as X=2, and "versicolor" as X=3.

data(iris) # this step is not always necessary, but ensures you're starting
# from the original version of a dataset stored in a loaded package
iris =

Table 2.26.: Summary statistics for the  $\tt iris$  data

	setosa	versicolor	virginica
	(N=50)	(N=50)	(N=50)
Sepal.Length			
Mean (SD)	$5.01 \ (0.352)$	5.94 (0.516)	6.59 (0.636)
Median [Min, Max]	5.00 [4.30, 5.80]	5.90 [4.90, 7.00]	6.50 [4.90, 7.90]
Sepal.Width			
Mean (SD)	3.43(0.379)	2.77(0.314)	2.97(0.322)
Median [Min, Max]	3.40 [2.30, 4.40]	2.80 [2.00, 3.40]	3.00 [2.20, 3.80]
Petal.Length			
Mean (SD)	1.46 (0.174)	4.26 (0.470)	5.55 (0.552)
Median [Min, Max]	1.50 [1.00, 1.90]	4.35 [3.00, 5.10]	5.55 [4.50, 6.90]
Petal.Width			
Mean (SD)	$0.246 \ (0.105)$	1.33(0.198)	2.03 (0.275)
Median [Min, Max]	0.200 [0.100, 0.600]	1.30 [1.00, 1.80]	2.00 [1.40, 2.50]

#### 2. Linear (Gaussian) Models

```
iris |>
  tibble() |>
 mutate(
   X = case_when(
     Species == "setosa" ~ 1,
     Species == "virginica" ~ 2,
     Species == "versicolor" ~ 3
   )
  )
iris |>
 distinct(Species, X) |>
print()
#> # A tibble: 3 x 2
#> Species
              X
#> <fct>
               <dbl>
#> 1 setosa
                   1
#> 2 versicolor
                   3
#> 3 virginica
                   2
```

Then we could fit a model like:

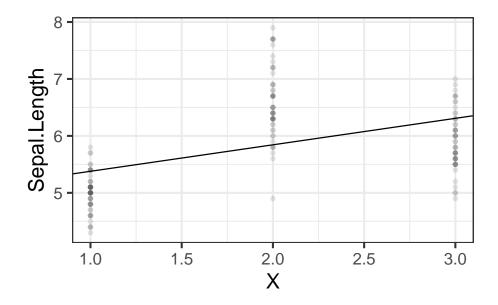
```
iris_lm1 = lm(Sepal.Length ~ X, data = iris)
iris_lm1 |> parameters() |> print_md()
```

Parameter	Coefficient	SE	95% CI	t(148)	p
$\overline{\text{(Intercept)}}$ X	4.91 0.47		(4.60, 5.23) (0.32, 0.61)		

## 2.10.3. Let's see how that model looks:

```
iris_plot1 = iris |>
    ggplot(
    aes(
        x = X,
        y = Sepal.Length)
) +
    geom_point(alpha = .1) +
    geom_abline(
    intercept = coef(iris_lm1)[1],
    slope = coef(iris_lm1)[2]) +
    theme_bw(base_size = 18)
```

#### print(iris\_plot1)



#### 2. Linear (Gaussian) Models

We have forced the model to use a straight line for the three estimated means. Maybe not a good idea?

## 2.10.4. Let's see what R does with categorical variables by default:

```
iris_lm2 = lm(Sepal.Length ~ Species, data = iris)
iris_lm2 |> parameters() |> print_md()
```

Parameter	Coefficient	SE	95% CI	t(147)	p
(Intercept)	5.01	0.07	(4.86, 5.15)	68.76	< .001
Species	0.93	0.10	(0.73, 1.13)	9.03	< .001
(versicolor)					
Species (virginica)	1.58	0.10	(1.38, 1.79)	15.37	< .001

## 2.10.5. Re-parametrize with no intercept

If you don't want the default and offset option, you can use "-1" like we've seen previously:

Parameter	Coefficient	SE	95% CI	t(147)	p
Species (setosa)	5.01	0.07	(4.86, 5.15)	68.76	< .001
Species (versicolor)	5.94	0.07	(5.79, 6.08)	81.54	< .001
Species (virginica)	6.59	0.07	(6.44, 6.73)	90.49	< .001

#### 2.10.6. Let's see what these new models look like:

```
iris_plot2 =
  iris |>
  mutate(
    predlm2 = predict(iris_lm2)) |>
  arrange(X) |>
  ggplot(aes(x = X, y = Sepal.Length)) +
  geom_point(alpha = .1) +
  geom_line(aes(y = predlm2), col = "red") +
  geom_abline(
    intercept = coef(iris_lm1)[1],
    slope = coef(iris_lm1)[2]) +
  theme_bw(base_size = 18)
```

```
print(iris_plot2)
```

## 2. Linear (Gaussian) Models



## 2.10.7. Let's see how R did that:

```
formula(iris_lm2)
#> Sepal.Length ~ Species
model.matrix(iris_lm2) |> as_tibble() |> unique()
```

(Intercept)	Speciesversicolor	Speciesvirginica
1	0	0
1	1	0
1	0	1

This is called a "corner point parametrization".

#### 2. Linear (Gaussian) Models

```
formula(iris.lm2b)
#> Sepal.Length ~ Species - 1
model.matrix(iris.lm2b) |> as_tibble() |> unique()
```

Speciessetosa	Speciesversicolor	Speciesvirginica
1	0	0
0	1	0
0	0	1

This can be called a "group point parametrization".

There are more options; see Dobson and Barnett (2018) §6.4.1 and the codingMatrices package<sup>5</sup> vignette<sup>6</sup> (Venables (2023)).

 $<sup>^{5} \</sup>rm https://CRAN.R\text{-}project.org/package=codingMatrices$ 

 $<sup>^{6}</sup> https://cran.r-project.org/web/packages/codingMatrices/vignettes/codingMatrices.\\ pdf$ 

Logistic regression and variations

#### **Acknowledgements**

This content is adapted from:

- Dobson and Barnett (2018), Chapter 7
- Vittinghoff et al. (2012), Chapter 5
- https://dmrocke.ucdavis.edu/Class/EPI204-Spring-2021/EPI204-Spring-2021.html

#### Configuring R

Functions from these packages will be used throughout this document:

```
library(pander) # format tables for markdown
library(ggplot2) # graphics
library(ggeasy) # help with graphics
library(dplyr) # manipulate data
library(haven) # import Stata files
library(knitr) # format R output for markdown
library(tidyr) # Tools to help to create tidy data
```

```
library(plotly) # interactive graphics
library(dobson) # datasets from Dobson and Barnett 2018
library(parameters) # format model output tables for markdown
library(conflicted) # check for conflicting function definitions
```

Here are some R settings I use in this document:

```
rm(list = ls()) # delete any data that's already loaded into R
knitr::opts_chunk$set(message = FALSE)
options('digits' = 4)
```

#### 3.1. Introduction

#### 3.1.1. What is logistic regression?

**Logistic regression** is a framework for modeling binary outcomes, conditional on one or more *predictors* (a.k.a. *covariates*).

Exercise 3.1 (Examples of binary outcomes). What are some examples of binary outcomes in the health sciences?

Solution. Examples of binary outcomes include:

- exposure (exposed vs unexposed)
- disease (diseased vs healthy)
- recovery (recovered vs unrecovered)
- relapse (relapse vs remission)
- return to hospital (returned vs not)
- vital status (dead vs alive)

Logistic regression uses the Bernoulli distribution to model the outcome variable, conditional on one or more covariates.

Exercise 3.2. Write down a mathematical definition of the Bernoulli distribution.

Solution. See Definition A.2.

#### 3.1.2. Logistic regression versus linear regression

Logistic regression differs from linear regression, which uses the Gaussian ("normal") distribution to model the outcome variable, conditional on the covariates.

**Exercise 3.3.** Recall: what kinds of outcomes is linear regression used for?

Solution. Linear regression is typically used for numerical outcomes that aren't event counts or waiting times for an event. Examples of outcomes that are often analyzed using linear regression include include weight, height, and income.

#### 3.2. Risk Estimation and Prediction

In Epi 203, you have already seen methods for modeling binary outcomes using one covariate that is also binary (such as exposure/non-exposure). In this section, we review one-covariate analyses, with a special focus on risk ratios and odds ratios, which are important concepts for interpreting logistic regression.

Example 3.1 (Oral Contraceptive Use and Heart Attack).

• Research question: how does oral contraceptive (OC) use affect the risk of myocardial infarction (MI; a.k.a. heart attack)?

This was an issue when oral contraceptives were first developed, because the original formulations used higher concentrations of hormones. Modern OCs don't have this issue.

Table 3.1 contains simulated data for an imaginary follow-up (a.k.a. *prospective*) study in which two groups are identified, one using OCs and another not using OCs, and both groups are tracked for three years to determine how many in each groups have MIs.

Table 3.1.: Simulated data from study of oral contraceptive use and heart attack risk

OC	MI	No MI	Total
OC use	13	4987	5000

Table 3.1.: Simulated data from study of oral contraceptive use and heart attack risk

OC	MI	No MI	Total
No OC use	7	9993	10000
Total	20	14980	15000

Exercise 3.4. Review: estimate the probabilities of MI for OC users and non-OC users in Example 3.1.

Solution.

$$\hat{p}(MI|OC) = \frac{13}{5000} = 0.0026$$

$$\hat{p}(MI|\neg OC) = \frac{7}{10000} = 7 \times 10^{-4}$$

## i Two meanings of "controls"

Depending on context, "controls" can mean either individuals who don't experience an *exposure* of interest, or individuals who don't experience an *outcome* of interest.

**Definition 3.1** (cases and controls in retrospective studies). In *retrospective studies*, participants who experience the outcome of interest are called **cases**, while participants who don't experience that outcome are called **controls**.

**Definition 3.2** (treatment groups and control groups in prospective studies). In *prospective studies*, the group of participants who experience the treatment or exposure of interest is called the **treatment group**, while the participants who receive the baseline or comparison treatment (for example, clinical trial participants who receive a placebo or a standard-of-care treatment rather than an experimental

treatment) are called controls.

#### 3.2.1. Comparing probabilities

#### 3.2.1.1. Risk differences

The simplest comparison of two probabilities,  $\pi_1$ , and  $\pi_2$ , is the difference of their values:

**Definition 3.3** (Risk difference). The **risk difference** of two probabilities,  $\pi_1$ , and  $\pi_2$ , is the difference of their values:

$$\delta(\pi_1,\pi_2) \stackrel{\mathrm{def}}{=} \pi_1 - \pi_2$$

**Example 3.2.** In Example 3.1, the estimated risk difference in MI risk between OC users and OC non-users is:

$$\begin{split} \hat{\delta}(\pi(OC), \pi(\neg OC)) &= \delta(\hat{\pi}(OC), \hat{\pi}(\neg OC)) \\ &= \hat{\pi}(OC) - \hat{\pi}(\neg OC) \\ &= 0.0026 - 7 \times 10^{-4} \\ &= 0.0019 \end{split}$$

#### 3.2.1.2. Risk ratios

**Definition 3.4** (Relative risk ratios). The **relative risk** of probability  $\pi_1$  compared to another probability  $\pi_2$ , also called the **risk ratio**, **relative risk ratio**, **probability ratio**, or **rate ratio**, is the ratio of those probabilities:

$$\rho(\pi_1,\pi_2) = \frac{\pi_1}{\pi_2}$$

**Example 3.3.** Above, we estimated that:

$$\hat{p}(MI|OC) = 0.0026$$

$$\hat{p}(MI|\neg OC) = 7 \times 10^{-4}$$

So we might estimate that the *relative risk* of MI for OC versus non-OC is:

rr = (13/5000)/(7/10000)

$$\begin{split} \hat{\rho}(OC, \neg OC) &= \frac{\hat{p}(MI|OC)}{\hat{p}(MI|\neg OC)} \\ &= \frac{0.0026}{7 \times 10^{-4}} \\ &= 3.71428571 \end{split}$$

We might summarize this result by saying that "the estimated probability of MI among OC users was 3.71428571 as high as the estimated probability among OC non-users.

Sometimes, we divide the risk difference by the comparison probability, or equivalently, subtract 1 from the risk ratio; the result is called the **relative risk difference**:

$$\begin{split} \xi(\pi_1,\pi_2) &= \frac{\pi_1 - \pi_2}{\pi_2} \\ &= \frac{\pi_1}{\pi_2} - 1 \end{split}$$

Risk differences, risk ratios, and relative risk differences are defined by two probabilities, plus a choice of which probability is the **baseline** or

**reference** probability (i.e., which probability is the subtrahend of the risk difference or the denominator of the risk ratio). To switch which one is the reference probability, invert the ratio and multiply the difference by -1.

**Example 3.4.** Above, we estimated that the risk ratio of OC versus non-OC is:

$$\rho(OC, \neg OC) = 3.71428571$$

In comparison, the risk ratio for non-OC versus OC is:

$$\begin{split} \rho(\neg OC, OC) &= \frac{\hat{p}(MI|\neg OC)}{\hat{p}(MI|OC)} \\ &= \frac{7 \times 10^{-4}}{0.0026} \\ &= 0.26923077 \\ &= \frac{1}{\rho(OC, \neg OC)} \end{split}$$

#### 3.2.2. Odds and probabilities

In logistic regression, we will make use of a transformation (rescaling) of probability, called odds.

**Definition 3.5** (Odds). The **odds** of an outcome A, denoted  $\omega(A)$  ("omega"), is the probability that the outcome occurs, divided by the probability that it doesn't occur:

$$\omega(A) = \frac{\Pr(A)}{\Pr(\neg A)}$$

**Theorem 3.1.** If the probability of an outcome A is  $Pr(A) = \pi$ , then the corresponding odds of A is

$$\omega(\pi) \stackrel{def}{=} \frac{\pi}{1 - \pi} \tag{3.1}$$

Proof.

$$\begin{split} \Pr(\neg A) &= 1 - \Pr(A) = 1 - \pi \\ &: \omega(A) \stackrel{\text{def}}{=} \frac{\Pr(A)}{\Pr(\neg A)} = \frac{\pi}{1 - \pi} \end{split}$$

[Function #eq-odds-probs], which transforms probabilities into odds, can be called the **odds function**. Figure 3.1 graphs the shape of this function.

:::

```
odds = function(pi) pi / (1 - pi)
library(ggplot2)
ggplot() +
  geom_function(fun = odds, aes(col = "odds function")) +
  xlim(0, .5) +
  xlab("Probability") +
  ylab("Odds") +
  geom_abline(aes(intercept = 0, slope = 1, col = "y=x")) +
  theme_bw() +
  labs(colour = "") +
  theme(legend.position = "bottom")
```

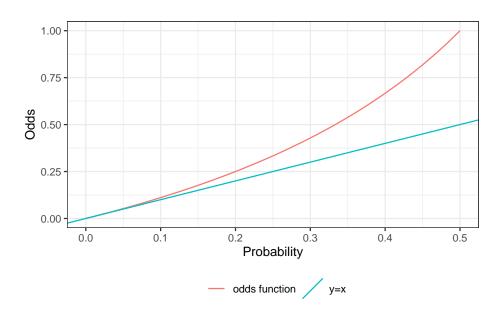


Figure 3.1.: Odds versus probability

**Example 3.5** (Calculating odds). In Exercise 3.4, we estimated that the probability of MI, given OC use, is  $\pi(OC) \stackrel{\text{def}}{=} \Pr(MI|OC) = 0.0026$ . If this estimate is correct, then the odds of MI, given OC use, is:

$$\omega(OC) \stackrel{\text{def}}{=} \frac{\Pr(MI|OC)}{\Pr(\neg MI|OC)}$$

$$= \frac{\Pr(MI|OC)}{1 - \Pr(MI|OC)}$$

$$= \frac{\pi(OC)}{1 - \pi(OC)}$$

$$= \frac{0.0026}{1 - 0.0026}$$

$$= 0.00260678$$

Exercise 3.5 (Calculating odds). Estimate the odds of MI, for non-OC users.

Solution.

$$\omega_(\neg OC) = 7.00490343 \times 10^{-4}$$

#### 3.2.2.1. A shortcut for calculating odds

The usual estimate for a probability of an event is "# events/# observations". We often denote # events as x and # observations as n. So:

$$\hat{\pi} = \frac{x}{n}$$

Thus, the usual estimate for the probability of a nonevent is:

$$1 - \hat{\pi} = 1 - \frac{x}{n}$$
$$= \frac{n}{n} - \frac{x}{n}$$
$$= \frac{n - x}{n}$$

Thus, the estimated odds is:

$$\frac{\hat{\pi}}{1 - \hat{\pi}} = \frac{\left(\frac{x}{n}\right)}{\left(\frac{n-x}{n}\right)} = \frac{x}{n-x}$$

That is, odds can be calculated directly as "# events" divided by "# nonevents" (without needing to calculate  $\hat{\pi}$  and  $1 - \hat{\pi}$  first).

**Example 3.6** (calculating odds using the shortcut). In Example 3.5, we calculated

$$\omega(OC)=0.00260678$$

Let's recalculate this result using our shortcut:

$$\omega(OC) = \frac{13}{5000 - 13}$$
$$= 0.00260678$$

Same answer!

#### 3.2.2.2. Odds of rare events

For rare events (small  $\pi$ ), odds and probabilities are nearly equal, because  $1 - \pi \approx 1$  (see Figure 3.1).

For example, in Example 3.5, the probability and odds differ by  $6.77762182 \times 10^{-6}$ .

**Exercise 3.6.** What odds value corresponds to the probability  $\pi = 0.2$ , and what is the numerical difference between these two values?

Solution.

$$\omega = \frac{\pi}{1 - \pi} = \frac{.2}{.8} = .25$$

#### 3.2.3. The inverse odds function

**Definition 3.6** (inverse odds function). The inverse odds function,

$$\pi(\omega) \stackrel{\text{def}}{=} \frac{\omega}{1+\omega}$$

converts odds into their corresponding probabilities (Figure 3.2).

The inverse-odds function takes an odds as input and produces a probability as output. Its domain of inputs is  $[0, \infty)$  and its range of outputs is [0, 1].

```
odds_inv = function(omega) (1 + omega^-1)^-1
ggplot() +
  geom_function(fun = odds_inv, aes(col = "inverse-odds")) +
  xlab("Odds") +
  ylab("Probability") +
  xlim(0,5) +
  ylim(0,1) +
  geom_abline(aes(intercept = 0, slope = 1, col = "x=y"))
```



Figure 3.2.: The inverse odds function,  $\pi(\omega)$ 

### Important

An equivalent expression for the inverse odds function is

$$\pi(\omega) = (1 - \omega^{-1})^{-1} \tag{3.2}$$

Exercise 3.7. Prove that Equation 3.2 is equivalent to Definition 3.6.

**Exercise 3.8.** What probability corresponds to an odds of  $\omega = 1$ , and what is the numerical difference between these two values?

Solution.

$$\pi(1) = \frac{1}{1+1} = \frac{1}{2} = .5$$

$$1 - \pi(1) = 1 - .5 = .5$$

#### 3.2.4. Odds ratios

Now that we have defined odds, we can introduce another way of comparing event probabilities: odds ratios.

**Definition 3.7** (Odds ratio). The **odds ratio** for two odds  $\omega_1, \, \omega_2$  is their ratio:

$$\theta(\omega_1,\omega_2) = \frac{\omega_1}{\omega_2}$$

**Example 3.7** (Calculating odds ratios). In Example 3.1, the odds ratio for OC users versus OC-non-users is:

$$\begin{aligned} \theta(\omega(OC), \omega(\neg OC)) &= \frac{\omega(OC)}{\omega(\neg OC)} \\ &= \frac{0.0026}{7 \times 10^{-4}} \\ &= 3.71428571 \end{aligned}$$

When the outcome is rare (i.e., its probability is small) for both groups being compared in an odds ratio, the odds of the outcome will be similar to the probability of the outcome, and thus the risk ratio will be similar to the odds ratio.

For example, in Example 3.1, the outcome is rare for both OC and non-OC participants, so the odds for both groups are similar to the corresponding probabilities, and the odds ratio is similar the risk ratio.

#### 3.2.4.1. A shortcut for calculating odds ratio estimates

The general form of a two-by-two table is shown in Table 3.2.

Table 3.2.: A generic 2x2 table

,		
Event	Non-Event	Total
a	b	a+b
$\mathbf{c}$	d	c+d
a+c	b+d	a+b+c+d
	a c	c d

From this table, we have:

- $\hat{\pi}(Event|Exposed) = a/(a+b)$
- $\hat{\pi}(\neg Event|Exposed) = b/(a+b)$
- $\hat{\omega}(Event|Exposed) = \frac{\left(\frac{a}{a+b}\right)}{\left(\frac{b}{a+b}\right)} = \frac{a}{b}$

- $\hat{\omega}(Event|\neg Exposed) = \frac{c}{d}$  (see Exercise 3.9)
- $\theta(Exposed, \neg Exposed) = \frac{\frac{a}{b}}{\frac{c}{d}} = \frac{ad}{bc}$

**Exercise 3.9.** Given Table 3.2, show that  $\hat{\omega}(Event|\neg Exposed) = \frac{c}{d}$ .

#### 3.2.4.2. Properties of odds ratios

Odds ratios have a special property: we can swap a covariate with the outcome, and the odds ratio remains the same.

**Example 3.8.** In Example 3.1, we have:

$$\begin{split} \theta(MI;OC) &\stackrel{\text{def}}{=} \frac{\omega(MI|OC)}{\omega(MI|\neg OC)} \\ &\stackrel{\text{def}}{=} \frac{\left(\frac{\Pr(MI|OC)}{\Pr(\neg MI|OC)}\right)}{\left(\frac{\Pr(MI|\neg OC)}{\Pr(\neg MI|\neg OC)}\right)} \\ &= \frac{\left(\frac{\Pr(MI,OC)}{\Pr(\neg MI,OC)}\right)}{\left(\frac{\Pr(MI,OC)}{\Pr(\neg MI,OC)}\right)} \\ &= \left(\frac{\Pr(MI,OC)}{\Pr(\neg MI,OC)}\right) \left(\frac{\Pr(\neg MI,\neg OC)}{\Pr(MI,\neg OC)}\right) \\ &= \left(\frac{\Pr(MI,OC)}{\Pr(MI,OC)}\right) \left(\frac{\Pr(\neg MI,\neg OC)}{\Pr(\neg MI,OC)}\right) \\ &= \left(\frac{\Pr(OC,MI)}{\Pr(\neg OC,MI)}\right) \left(\frac{\Pr(\neg OC,\neg MI)}{\Pr(OC,\neg MI)}\right) \\ &= \left(\frac{\Pr(OC|MI)}{\Pr(\neg OC|MI)}\right) \left(\frac{\Pr(\neg OC|\neg MI)}{\Pr(OC|\neg MI)}\right) \\ &= \frac{\left(\frac{\Pr(OC|MI)}{\Pr(\neg OC|MI)}\right)}{\left(\frac{\Pr(OC|\neg MI)}{\Pr(\neg OC|\neg MI)}\right)} \\ &\stackrel{\text{def}}{=} \frac{\omega(OC|MI)}{\omega(OC|\neg MI)} \\ &\stackrel{\text{def}}{=} \theta(OC;MI) \end{split}$$

**Exercise 3.10.** For Table 3.2, show that  $\hat{\theta}(Exposed, Unexposed) = \hat{\theta}(Event, \neg Event)$ .

## 3.2.5. Effect of study design

Table 3.1 simulates a follow-up study in which two populations were followed and the number of MI's was observed. The risks are P(MI|OC) and  $P(MI|\neg OC)$  and we can estimate these risks from the data.

But suppose we had a case-control study in which we had 100 women with MI and selected a comparison group of 100 women without MI (matched as groups on age, etc.). Then MI is not random, and we cannot compute P(MI|OC) and we cannot compute the risk ratio. However, the odds ratio however can be computed.

The disease odds ratio is the odds for the disease in the exposed group divided by the odds for the disease in the unexposed group, and we cannot validly compute and use these separate parts.

But we can validly compute and use the exposure odds ratio, which is the odds for exposure in the disease group divided by the odds for exposure in the non-diseased group (because exposure can be treated as random):

$$\hat{\theta}(OC|MI) = \frac{\hat{\omega}(OC|MI)}{\hat{\omega}(OC|\neg MI)}$$

And these two odds ratios,  $\hat{\theta}(MI|OC)$  and  $\hat{\theta}(OC|MI)$  are mathematically equivalent, as we saw in Section 3.2.4.2.

Exercise 3.11. Calculate the odds ratio of MI with respect to OC use, assuming that Table 3.1 comes from a case-control study. Confirm that the result is the same as in Example 3.7.

Solution.

- $\omega(OC|MI) = P(OC|MI)/(1-P(OC|MI)) = \frac{13}{7} = 1.85714286$
- $\omega(OC|\neg MI) = P(OC|\neg MI)/(1-P(OC|\neg MI) = \frac{4987}{9993} = 0.49904933$
- $\theta(OC, MI) = \frac{\omega(OC|MI)}{\omega(OC|\neg MI)} = \frac{13/7}{4987/9993} = 3.72136125$

This is the same estimate we calculated in Example 3.7.

#### 3.2.5.1. Cross-Sectional Studies

- If a cross-sectional study is a probability sample of a population (which it rarely is) then we can estimate risks.
- If it is a sample, but not an unbiased probability sample, then we need to treat it in the same way as a case-control study.
- We can validly estimate odds ratios in either case.
- But we can usually not validly estimate risks and risk ratios.

## 3.3. Introduction to logistic regression

- In Example 3.1, we estimated the risk and the odds of MI for two discrete cases, as to whether of not the individual used oral contraceptives.
- If the predictor is quantitative (dose) or there is more than one predictor, the task becomes more difficult.
- In this case, we will use logistic regression, which is a generalization of the linear regression models you have been using that can account for a binary response instead of a continuous one.

#### 3.3.1. Binary outcomes models - one group, no covariates

$$\begin{split} p(Y=1) &= \pi \\ p(Y=0) &= 1 - \pi \\ p(Y=y) &= \pi^y (1-\pi)^{1-y} \\ \mathbf{y} &= (y_1, ..., y_n) \\ \mathcal{L}(\pi; \mathbf{y}) &= \pi^{\sum y_i} (1-\pi)^{n-\sum y_i} \\ \ell(\pi, \mathbf{y}) &= \left(\sum y_i\right) \log \left\{\pi\right\} + \left(n - \sum y_i\right) \log \left\{1 - \pi\right\} \\ &= \left(\sum y_i\right) \left(\log \left\{\pi\right\} - \log \left\{1 - \pi\right\}\right) + n \cdot \log \left\{1 - \pi\right\} \\ &= \left(\sum y_i\right) \log \left\{\frac{\pi}{1-\pi}\right\} + n \cdot \log \left\{1 - \pi\right\} \end{split}$$

### 3.3.2. Binary outcomes - general

$$\begin{split} p(Y_i = 1) &= \pi_i \\ p(Y_i = 0) &= 1 - \pi_i \\ p(Y_i = y) &= (\pi_i)^y (1 - \pi_i)^{1 - y} \\ \mathbf{y} &= (y_1, ..., y_n) \\ \mathcal{L}(\pi; \mathbf{y}) &= \prod_{i=1}^n (\pi_i)^{y_i} (1 - \pi_i)^{1 - y_i} \\ \ell(\pi, \mathbf{y}) &= \sum_{i=1}^n y_i \log \left\{ \pi_i \right\} + (1 - y_i) \log \left\{ 1 - \pi_i \right\} \end{split}$$

## 3.3.3. Modeling $\pi_i$ as a function of $X_i$

If there are only a few distinct  $X_i$  values, we can model each one separately.

Otherwise, we need regression.

$$\pi(x) \equiv \mathcal{E}(Y = 1|X = x)$$
$$= f(x^{\top}\beta)$$

Typically, we use  $f(\eta) = \text{expit}(\eta)$ .

**Definition 3.8** (expit function). The **expit** function (Figure 3.3), also known as the **inverse-logit** or **logistic** function, is:

$$\begin{aligned} \operatorname{expit}(\eta) &\stackrel{\text{def}}{=} \frac{\exp\{\eta\}}{1 + \exp\{\eta\}} \\ &= (1 + \exp\{-\eta\})^{-1} \end{aligned}$$

```
expit = function(eta) exp(eta)/(1+exp(eta))
library(ggplot2)
expit_plot =
    ggplot() +
    geom_function(fun = expit) +
    xlim(-5, 5) +
    ylim(0,1) +
    ylab(expression(expit(eta))) +
    xlab(expression(eta)) +
    theme_bw()
print(expit_plot)
```



Figure 3.3.: The expit function

**Definition 3.9** (logit function). The inverse of the expit function is the logit function:

$$g(p) = f^{-1}(p) = \operatorname{logit}(p) = \log\left\{\frac{p}{1-p}\right\}$$

```
logit = function(p) log(odds(p))

logit_plot =
    ggplot() +
    geom_function(fun = logit) +
    xlim(.01, .99) +
    ylab("logit(p)") +
    xlab("p") +
```

# theme\_bw() print(logit\_plot)

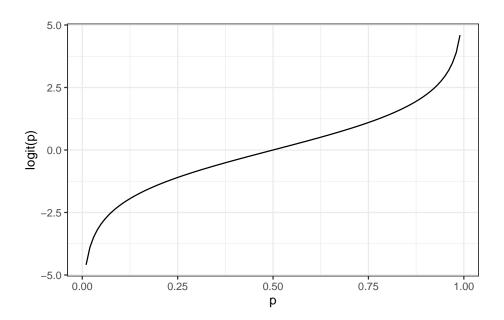


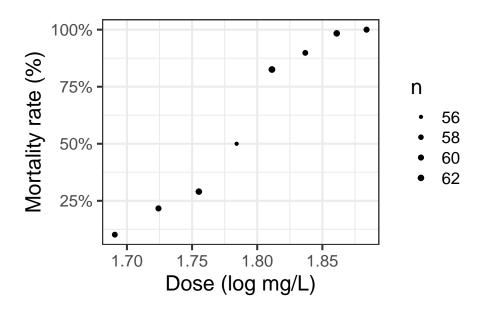
Figure 3.4.: the logit function

## 3.3.4. Diagram of expit and logit

$$\left[\pi \overset{\text{def}}{=} \Pr(Y=1)\right] \underbrace{\underbrace{\frac{\frac{\pi}{1-\pi}}{\frac{1-\pi}{1+\omega}} \left[\omega \overset{\text{def}}{=} \operatorname{odds}(Y=1)\right] \overset{\log\{\omega\}}{\underset{\exp\{\eta\}}{\longleftarrow}}}_{\text{exp}\{\eta\}} \left[\eta \overset{\text{def}}{=} \operatorname{log-odds}(Y=1)\right]$$

#### 3.3.5. Meet the beetles

```
library(glmx)
data(BeetleMortality, package = "glmx")
beetles = BeetleMortality |>
 mutate(
   pct = died/n,
   survived = n - died
  )
plot1 =
 beetles |>
 ggplot(aes(x = dose, y = pct)) +
 geom_point(aes(size = n)) +
  xlab("Dose (log mg/L)") +
 ylab("Mortality rate (%)") +
  scale_y_continuous(labels = scales::percent) +
  scale_size(range = c(1,2)) +
  theme_bw(base_size = 18)
print(plot1)
```



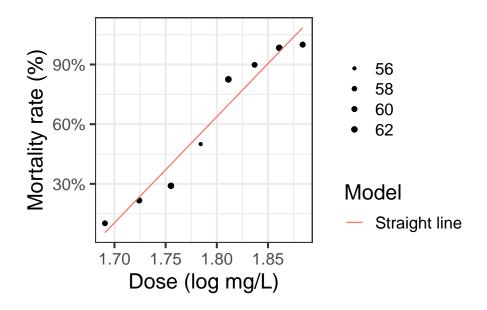
Mortality rates of adult flour beetles after five hours' exposure to gaseous carbon disulphide (Bliss 1935)

## 3.3.6. Why don't we use linear regression?

```
beetles_glm_grouped = beetles |>
  glm(formula = cbind(died, survived) ~ dose, family = "binomial")

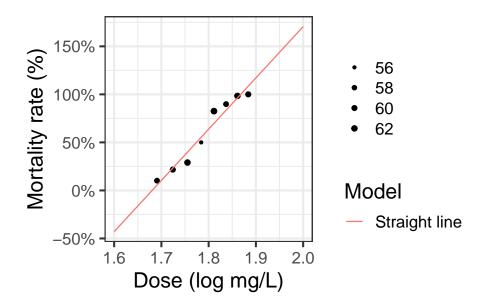
lm1 =
  beetles |>
  reframe(
    .by = everything(),
    outcome = c(
```

```
rep(1, times = died),
     rep(0, times = survived))
 ) |>
 lm(
   formula = outcome ~ dose,
   data = _)
lm2 =
 beetles |>
 reframe(
   .by = everything(),
   outcome = c(
     rep(1, times = died),
     rep(0, times = survived))
 ) |>
 lm(
   formula = outcome ~ log(dose),
   data = _)
range1 = range(beetles$dose) + c(-.2, .2)
f = function(x) predict(beetles_glm_grouped, newdata = data.frame(dose = x), type =
f.linear = function(x) predict(lm1, newdata = data.frame(dose = x))
f.linearlog = function(x) predict(lm2, newdata = data.frame(dose = x))
plot2 =
 plot1 +
 geom_function(
   fun = f.linear,
   aes(col = "Straight line")) +
 labs(colour="Model", size = "")
plot2 |> print()
```



## 3.3.7. Zoom out

```
(plot2 + expand_limits(x = c(1.6, 2))) |> print()
```



## 3.3.8. log transformation of dose?

```
plot3 = plot2 +
  expand_limits(x = c(1.6, 2)) +
  geom_function(fun = f.linearlog, aes(col = "Log-transform dose"))
(plot3 + expand_limits(x = c(1.6, 2))) |> print()
```



## 3.3.9. Logistic regression

```
plot4 = plot3 + geom_function(fun = f, aes(col = "Logistic regression"))
plot4 |> print()
```



#### 3.3.10. Three parts to regression models

- What distribution does the outcome have for a specific subpopulation defined by covariates? (outcome model)
- How does the combination of covariates relate to the mean? (link function)
- How do the covariates combine? (linear predictor, interactions)

#### 3.3.11. Logistic regression in R

```
beetles_glm_grouped =
  beetles |>
```

```
glm(
   formula = cbind(died, survived) ~ dose,
   family = "binomial")

beetles_glm_grouped |>
   parameters() |>
   print_md()
```

Parameter	Log-Odds	SE	95% CI	Z	р
$     \frac{\text{(Intercept)}}{\text{dose}} $	-60.72 34.27		(-71.44, -51.08) (28.85, 40.30)		

#### Fitted values:

```
fitted.values(beetles_glm_grouped)
    1
                              3
#> 0.058601026 0.164027869 0.362119006 0.605314906 0.795171772 0.903235819
  7
#> 0.955196107 0.979049344
predict(beetles_glm_grouped, type = "response")
#> 1 2 3
#> 0.058601026 0.164027869 0.362119006 0.605314906 0.795171772 0.903235819
     7
#> 0.955196107 0.979049344
predict(beetles_glm_grouped, type = "link")
#> 1 2 3
                                                            6
#> -2.77661484 -1.62855893 -0.56617883 0.42766061 1.35638644 2.23370678
#>
         7
#> 3.05962163 3.84441209
fit_y = beetles$n * fitted.values(beetles_glm_grouped)
```

### 3.3.12. Individual observations

```
beetles_long =
 beetles |>
 reframe(
   .by = everything(),
   outcome = c(
     rep(1, times = died),
     rep(0, times = survived))
 )
beetles_long |> tibble() |> print()
#> # A tibble: 481 x 6
#>
      dose died n pct survived outcome
     <dbl> <int> <int> <dbl>
                                     <dbl>
                             <int>
#>
  1 1.69 6 59 0.102
                                53
  2 1.69
             6 59 0.102
                                53
                                         1
#>
  3 1.69 6 59 0.102
#>
                                53
                                         1
#> 4 1.69 6 59 0.102
#> 5 1.69 6 59 0.102
                                53
                                         1
                               53
                                         1
  6 1.69 6 59 0.102
                                         1
#>
                               53
#> 7 1.69 6 59 0.102
                                53
                                         0
#> 8 1.69 6 59 0.102
                                53
                                         0
#> 9 1.69 6 59 0.102
                                53
                                         0
#> 10 1.69
              6
                   59 0.102
                                53
                                         0
#> # i 471 more rows
```

Here's the model with individual data

```
beetles_glm_ungrouped =
  beetles_long |>
  glm(
```

```
formula = outcome ~ dose,
  family = "binomial")

beetles_glm_ungrouped |> parameters() |> print_md()
```

Parameter	Log-Odds	SE	95% CI	Z	p
$     \hline     (Intercept) \\     dose $	-60.72 34.27		(-71.44, -51.08) (28.85, 40.30)		

Here's the previous version again:

```
beetles_glm_grouped |> parameters() |> print_md()
```

Parameter	Log-Odds	SE	95% CI	${f z}$	р
(Intercept) dose	-60.72 34.27		(-71.44, -51.08) (28.85, 40.30)		

They seem the same! But not quite:

```
logLik(beetles_glm_grouped)
#> 'log Lik.' -18.715135 (df=2)
logLik(beetles_glm_ungrouped)
#> 'log Lik.' -186.2354 (df=2)
```

The difference is due to the binomial coefficient  $\binom{n}{x}$  which isn't included in the individual-observations (Bernoulli) version of the model.

# 3.4. Multiple logistic regression

### 3.4.1. Coronary heart disease (WCGS) study data

Let's use the data from the following study to explore multiple logistic regression:

#### 3.4.1.1. Summary of study

From Vittinghoff et al. (2012):

"The Western Collaborative Group Study (WCGS) was a large epidemiological study designed to investigate the association between the "type A" behavior pattern and coronary heart disease (CHD) (Rosenman et al. 1964)."

From Wikipedia, "Type A and Type B personality theory":

"The hypothesis describes Type A individuals as outgoing, ambitious, rigidly organized, highly status-conscious, impatient, anxious, proactive, and concerned with time management....

The hypothesis describes Type B individuals as a contrast to those of Type A. Type B personalities, by definition, are noted to live at lower stress levels. They typically work steadily and may enjoy achievement, although they have a greater tendency to disregard physical or mental stress when they do not achieve."

### 3.4.1.2. Study design

from ?faraway::wcgs:

3154 healthy young men aged 39-59 from the San Francisco area were assessed for their personality type. All were free from coronary heart

disease at the start of the research. Eight and a half years later change in CHD status was recorded.

#### Details (from faraway::wcqs)

The WCGS began in 1960 with 3,524 male volunteers who were employed by 11 California companies. Subjects were 39 to 59 years old and free of heart disease as determined by electrocardiogram. After the initial screening, the study population dropped to 3,154 and the number of companies to 10 because of various exclusions. The cohort comprised both blue- and white-collar employees.

At baseline the following information was collected:

- socio-demographic including:
- age
- education
- marital status
- income
- occupation
- physical and physiological including:
- height
- weight
- blood pressure
- electrocardiogram
- corneal arcus;
- biochemical including:
- cholesterol and lipoprotein fractions;
- medical and family history and use of medications;
- behavioral data including
- Type A interview,
- smoking,
- exercise
- alcohol use.

Later surveys added data on:

- anthropometry
- triglycerides
- Jenkins Activity Survey
- caffeine use

Average follow-up continued for 8.5 years with repeat examinations.

Reference: Coronary Heart Disease in the Western Collaborative Group Study Final Follow-up Experience of 8 1/2 Years Ray H. Rosenman, MD; Richard J. Brand, PhD; C. David Jenkins, PhD; Meyer Friedman, MD; Reuben Straus, MD; Moses Wurm, MD JAMA. 1975;233(8):872-877. doi:10.1001/jama.1975.03260080034016.

#### 3.4.2. Load the data

Here, I load the data:

## 3.4.3. Now let's do some data cleaning

```
library(arsenal) # provides `set_labels()`
wcgs = wcgs |>
 mutate(
    age = age |>
      arsenal::set_labels("Age (years)"),
    arcus =
      arcus |>
      as.logical() |>
      arsenal::set_labels("Arcus Senilis"),
    time169 =
      time169 |>
      as.numeric() |>
      arsenal::set_labels("Observation (follow up) time (days)"),
    dibpat =
      dibpat |>
      as_factor() |>
      relevel(ref = "Type A") |>
      arsenal::set_labels("Behavioral Pattern"),
    typchd69 = typchd69 |>
      labelled(
        label = "Type of CHD Event",
        labels =
          c(
            "None" = 0,
            "infdeath" = 1,
            "silent" = 2,
```

```
"angina" = 3)),

# turn stata-style labelled variables in to R-style factors:
across(
    where(is.labelled),
    haven::as_factor)
)
```

#### 3.4.4. What's in the data

Here's a table of the data:

```
wcgs |>
select(-c(id, uni, t1)) |>
tableby(chd69 ~ ., data = _) |>
summary(
    pfootnote = TRUE,
    title =
        "Baseline characteristics by CHD status at end of follow-up")
```

Table 3.6.: Baseline characteristics by CHD status at end of follow-up

	No (N=2897)	Yes (N=257)	Total (N=3154)	p value
Age (years)				<
_				$0.001^{1}$
Mean (SD)	46.082	48.490	46.279	
` ,	(5.457)	(5.801)	(5.524)	
Range	39.000 -	39.000 -	39.000 -	
-	59.000	59.000	59.000	

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	No	Yes	Total	p
	(N=2897)	(N=257)	(N=3154)	value
Arcus Senilis				<
				$0.001^{2}$
N-Miss	0	2	2	
FALSE	2058	153	2211	
	(71.0%)	(60.0%)	(70.1%)	
TRUE	839	102	941	
	(29.0%)	(40.0%)	(29.9%)	
Behavioral Pattern				<
				$0.001^2$
A1	234~(8.1%)	$30\ (11.7\%)$	264~(8.4%)	
A2	1177	148	1325	
	(40.6%)	(57.6%)	(42.0%)	
B3	1155	$61\ (23.7\%)$	1216	
	(39.9%)		(38.6%)	
B4	331	$18 \ (7.0\%)$	349	
	(11.4%)		(11.1%)	
Body Mass Index				<
(kg/m2)				$0.001^{1}$
Mean (SD)	24.471	25.055	24.518	
	(2.561)	(2.579)	(2.567)	
Range	11.191 -	19.225 -	11.191 -	
	37.653	38.947	38.947	
Total Cholesterol				<
				$0.001^{1}$
N-Miss	12	0	12	
Mean (SD)	224.261	250.070	226.372	
	(42.217)	(49.396)	(43.420)	
Range	103.000 -	155.000 -	103.000 -	
	400.000	645.000	645.000	
Diastolic Blood				<
Pressure				$0.001^{1}$

	No (N=2897)	Yes (N=257)	Total (N=3154)	p value
Mean (SD)	81.723	85.315	82.016	
(15)	(9.621)	(10.311)	(9.727)	
Range	58.000 -	64.000 -	58.000 -	
	150.000	122.000	150.000	
Behavioral Pattern				<
				$0.001^{2}$
Type A	1411	178	1589	
	(48.7%)	(69.3%)	(50.4%)	
Type B	1486	79 (30.7%)	1565	
	(51.3%)	,	(49.6%)	
Height (inches)	, ,		,	$0.290^{1}$
Mean (SD)	69.764	69.938	69.778	
, ,	(2.539)	(2.410)	(2.529)	
Range	60.000 -	63.000 -	60.000 -	
	78.000	77.000	78.000	
Ln of Systolic				<
Blood Pressure				$0.001^{1}$
Mean (SD)	4.846	4.900	4.850	
	(0.110)	(0.125)	(0.112)	
Range	4.585 -	4.605 -	4.585 -	
	5.438	5.298	5.438	
Ln of Weight				<
				$0.001^{1}$
Mean (SD)	5.126	5.155	5.128	
	(0.123)	(0.118)	(0.123)	
Range	4.357 -	4.868 -	4.357 -	
	5.670	5.768	5.768	
Cigarettes per day				<
				$0.001^{1}$
Mean (SD)	11.151	16.665	11.601	
	(14.329)	(15.657)	(14.518)	

	No	Yes	Total	p
	(N=2897)	(N=257)	(N=3154)	value
Range	0.000 -	0.000 -	0.000 -	
_	99.000	60.000	99.000	
Systolic Blood				<
Pressure				$0.001^{1}$
Mean (SD)	128.034	135.385	128.633	
	(14.746)	(17.473)	(15.118)	
Range	98.000 -	100.000 -	98.000 -	
	230.000	200.000	230.000	
Current smoking				<
				$0.001^{2}$
No	1554	98 (38.1%)	1652	
	(53.6%)		(52.4%)	
Yes	1343	159	1502	
	(46.4%)	(61.9%)	(47.6%)	
Observation (follow				<
up) time (days)				$0.001^{1}$
Mean (SD)	2775.158	1654.700	2683.859	
	(562.205)	(859.297)	(666.524)	
Range	238.000 -	18.000 -	18.000 -	
	3430.000	3229.000	3430.000	
Type of CHD				
Event				
None	0 (0.0%)	0 (0.0%)	0 (0.0%)	
infdeath	2897	$0\ (0.0\%)$	2897	
	(100.0%)		(91.9%)	
silent	0 (0.0%)	135	135 (4.3%)	
	,	(52.5%)	,	
angina	0 (0.0%)	71(27.6%)	$71\ (2.3\%)$	
4	0(0.0%)	51 (19.8%)	51 (1.6%)	
Weight (lbs)	, ,	` /	` ,	<
. , ,				$0.001^{1}$

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	No	Yes	Total	p
	(N=2897)	(N=257)	(N=3154)	value
Mean (SD)	169.554	174.463	169.954	
	(21.010)	(21.573)	(21.096)	
Range	78.000 -	130.000 -	78.000 -	
	290.000	320.000	320.000	
Weight Category				<
				$0.001^{2}$
< 140	$217 \ (7.5\%)$	15 (5.8%)	$232 \ (7.4\%)$	
140-170	1440	98 (38.1%)	1538	
	(49.7%)		(48.8%)	
170-200	1049	122	1171	
	(36.2%)	(47.5%)	(37.1%)	
> 200	191~(6.6%)	22~(8.6%)	213~(6.8%)	
RECODE of age				<
(Age)				$0.001^{2}$
35-40	512	$31\ (12.1\%)$	543	
	(17.7%)		(17.2%)	
41-45	1036	55~(21.4%)	1091	
	(35.8%)		(34.6%)	
46-50	680	70~(27.2%)	750	
	(23.5%)		(23.8%)	
51-55	463	65~(25.3%)	528	
	(16.0%)		(16.7%)	
56-60	$206 \ (7.1\%)$	$36 \ (14.0\%)$	$242 \ (7.7\%)$	

- 1. Linear Model ANOVA
- 2. Pearson's Chi-squared test

## 3.4.5. Data by age and personality type

For now, we will look at the interaction between age and personality type (dibpat). To make it easier to visualize the data, we summarize the event rates for each combination of age:

```
chd_grouped_data =
  wcgs |>
  summarize(
    .by = c(age, dibpat),
    n = n(),
    `p(chd)` = mean(chd69 == "Yes") |>
        labelled(label = "CHD Event by 1969"),
    `odds(chd)` = `p(chd)`/(1-`p(chd)`),
    `logit(chd)` = log(`odds(chd)`)
)

chd_grouped_data
```

age	dibpat	n	p(chd)	odds(chd)	logit(chd)
50	Type A	76	0.105263	0.1176	-2.140
51	Type A	67	0.164179	0.1964	-1.627
59	Type A	30	0.233333	0.3043	-1.190
44	Type A	113	0.079646	0.0865	-2.447
47	Type A	72	0.097222	0.1077	-2.228
40	Type A	133	0.067669	0.0726	-2.623
41	Type A	108	0.064815	0.0693	-2.669
43	Type A	97	0.072165	0.0778	-2.554
54	Type A	53	0.132075	0.1522	-1.883
48	Type A	80	0.150000	0.1765	-1.735
39	Type A	128	0.085938	0.0940	-2.364
49	Type A	67	0.238806	0.3137	-1.159

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age	dibpat	n	p(chd)	odds(chd)	logit(chd)
55	Type A	55	0.163636	0.1957	-1.631
56	Type A	49	0.244898	0.3243	-1.126
42	Type A	101	0.039604	0.0412	-3.188
45	Type A	77	0.090909	0.1000	-2.303
46	Type A	91	0.065934	0.0706	-2.651
57	Type A	31	0.129032	0.1481	-1.909
53	Type A	62	0.112903	0.1273	-2.061
52	Type A	65	0.200000	0.2500	-1.386
58	Type A	34	0.147059	0.1724	-1.758
45	Type B	109	0.045872	0.0481	-3.035
41	Type B	125	0.040000	0.0417	-3.178
47	Type B	75	0.013333	0.0135	-4.304
39	Type B	138	0.057971	0.0615	-2.788
49	Type B	67	0.074627	0.0806	-2.518
51	Type B	56	0.107143	0.1200	-2.120
42	Type B	121	0.008264	0.0083	-4.787
50	Type B	59	0.050847	0.0536	-2.927
44	Type B	122	0.032787	0.0339	-3.384
56	Type B	27	0.000000	0.0000	-Inf
40	Type B	144	0.020833	0.0213	-3.850
58	Type B	22	0.045455	0.0476	-3.045
48	Type B	84	0.083333	0.0909	-2.398
43	Type B	118	0.050847	0.0536	-2.927
53	Type B	43	0.116279	0.1316	-2.028
54	Type B	54	0.074074	0.0800	-2.526
46	Type B	79	0.063291	0.0676	-2.695
52	Type B	48	0.041667	0.0435	-3.135
55	Type B	25	0.040000	0.0417	-3.178
57	Type B	32	0.093750	0.1034	-2.269
59	Type B	17	0.235294	0.3077	-1.179

## 3.4.6. Graphical exploration

### 3.4.6.1. Probability scale

```
library(ggplot2)
library(ggeasy)
library(scales)
chd_plot_probs =
  chd_grouped_data |>
  ggplot(
    aes(
      x = age,
     y = p(chd),
      col = dibpat)
  geom_point(aes(size = n), alpha = .7) +
  scale_size(range = c(1,4)) +
  geom_line() +
  theme_bw() +
  ylab("P(CHD Event by 1969)") +
  scale_y_continuous(
    labels = scales::label_percent(),
    sec.axis = sec_axis(
      ~ odds(.),
      name = "odds(CHD Event by 1969)")) +
  ggeasy::easy_labs() +
  theme(legend.position = "bottom")
```

```
print(chd_plot_probs)
```



Figure 3.5.: CHD rates by age group, probability scale

### 3.4.6.2. Odds scale

```
trans_odds = trans_new(
  name = "odds",
  transform = odds,
  inverse = odds_inv)

chd_plot_probs +
  scale_y_continuous(
    trans = trans_odds,
    name = paste(chd_plot_probs$labels$y, "(odds spacing)"),
    sec.axis = sec_axis(
```

```
~ odds(.),
     name = "odds(CHD Event by 1969)"))
chd_plot_odds =
 chd_grouped_data |>
 ggplot(
   aes(
     x = age,
     y = `odds(chd)`,
     col = dibpat)
 ) +
 geom_point(aes(size = n), alpha = .7) +
 scale_size(range = c(1,4)) +
 geom_line() +
 theme_bw() +
 ylab("odds(CHD Event by 1969)") +
 ggeasy::easy_labs()
```

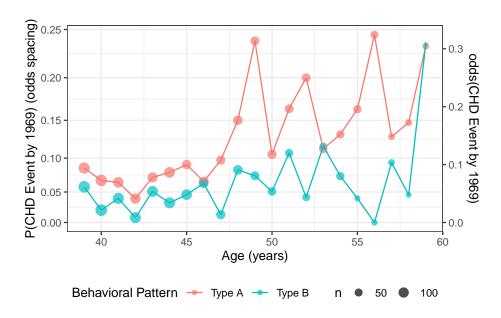


Figure 3.6.: CHD rates by age group, odds scale

print(chd\_plot\_odds)



## 3.4.6.3. Log-odds (logit) scale

```
chd_plot_logit =
  chd_grouped_data |>
  ggplot(
    aes(
        x = age,
        y = `logit(chd)`,
        col = dibpat)
  ) +
  geom_point(aes(size = n), alpha = .7) +
  scale_size(range = c(1,4)) +
  geom_line() +
  theme_bw() +
```

```
ylab("log{odds(CHD Event by 1969)}") +
ggeasy::easy_labs()
print(chd_plot_logit)
```



Figure 3.7.: CHD data (logit-scale)

# 3.4.7. Logistic regression models for CHD data

Here, we fit stratified models for CHD by personality type.

```
chd_glm_strat = glm(
  "formula" = chd69 == "Yes" ~ dibpat + dibpat:age - 1,
  "data" = wcgs,
```

```
"family" = binomial(link = "logit")
)
chd_glm_strat |> parameters() |> print_md()
```

	Log-				
Parameter	Odds	SE	95% CI	${f z}$	p
dibpat (Type A)	-5.50	0.67	(-6.83, -4.19)	-8.18	< .001
dibpat (Type B)	-5.80	0.98	(-7.73, -3.90)	-5.95	< .001
dibpat (Type A) $\times$	0.07	0.01	(0.05, 0.10)	5.24	< .001
age					
dibpat (Type B) $\times$	0.06	0.02	(0.02, 0.10)	3.01	0.003
age					

We can get the corresponding odds ratios  $(e^{\beta}s)$  by passing exponentiate = TRUE to parameters():

```
chd_glm_strat |>
  parameters(exponentiate = TRUE) |>
  print_md()
```

Table 3.9.: Odds ratio estimates for CHD model

	Odds				
Parameter	Ratio	SE	95% CI	${f z}$	p
dibpat (Type A)	4.09e-03	2.75e-	(1.08e-03,	-8.18	<
		03	0.02)		.001
dibpat (Type B)	3.02e-03	2.94e-	(4.40e-04,	-5.95	<
		03	0.02)		.001

Table 3.9.: Odds ratio estimates for CHD model

	Odds				
Parameter	Ratio	SE	95% CI	${f z}$	p
dibpat (Type A)	1.07	0.01	(1.05, 1.10)	5.24	<
$\times$ age					.001
dibpat (Type B)	1.06	0.02	(1.02, 1.11)	3.01	0.003
$\times$ age					

### 3.4.8. Models superimposed on data

We can graph our fitted models on each scale (probability, odds, log-odds).

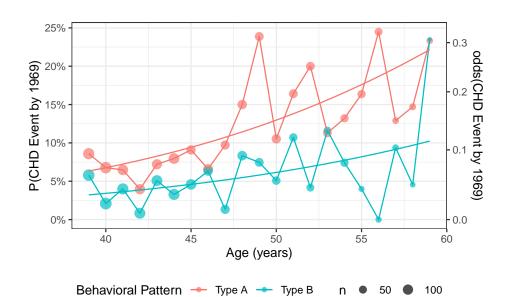
### 3.4.8.1. probability scale

```
curve_type_A = function(x)
{
   chd_glm_strat |> predict(
       type = "response",
       newdata = tibble(age = x, dibpat = "Type A"))
}

curve_type_B = function(x)
{
   chd_glm_strat |> predict(
      type = "response",
      newdata = tibble(age = x, dibpat = "Type B"))
}
```

```
chd_plot_probs_2 =
  chd_plot_probs +
  geom_function(
    fun = curve_type_A,
    aes(col = "Type A")
) +
  geom_function(
    fun = curve_type_B,
    aes(col = "Type B")
)
```

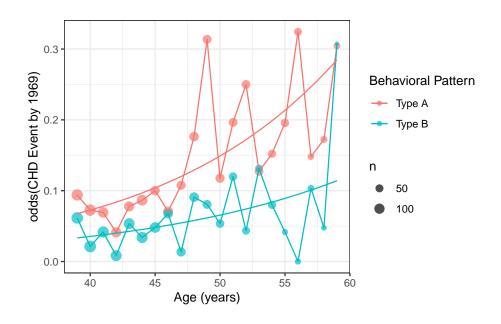
# print(chd\_plot\_probs\_2)



### 3.4.8.2. odds scale

```
curve_type_A = function(x)
 chd_glm_strat |> predict(
   type = "link",
   newdata = tibble(age = x, dibpat = "Type A")) |> exp()
}
curve_type_B = function(x)
 chd_glm_strat |> predict(
   type = "link",
   newdata = tibble(age = x, dibpat = "Type B")) |> exp()
}
chd_plot_odds_2 =
 chd_plot_odds +
 geom_function(
   fun = curve_type_A,
   aes(col = "Type A")
 ) +
 geom_function(
   fun = curve_type_B,
   aes(col = "Type B")
```

```
print(chd_plot_odds_2)
```

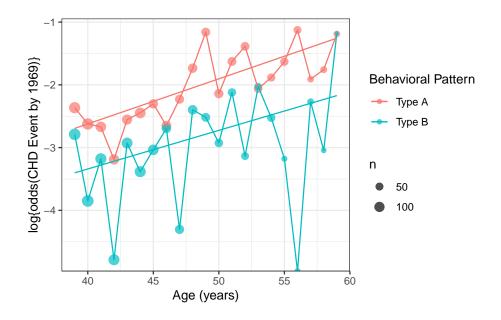


### 3.4.8.3. log-odds (logit) scale

```
curve_type_A = function(x)
{
   chd_glm_strat |> predict(
      type = "link",
      newdata = tibble(age = x, dibpat = "Type A"))
}
curve_type_B = function(x)
{
   chd_glm_strat |> predict(
      type = "link",
      newdata = tibble(age = x, dibpat = "Type B"))
}
```

```
chd_plot_logit_2 =
  chd_plot_logit +
  geom_function(
    fun = curve_type_A,
    aes(col = "Type A")
) +
  geom_function(
    fun = curve_type_B,
    aes(col = "Type B")
)
```

# print(chd\_plot\_logit\_2)



# 3.4.9. reference-group and contrast parametrization

We can also use the corner-point parametrization (with reference groups and contrasts):

```
chd_glm_contrasts =
  wcgs |>
  glm(
    "data" = _,
    "formula" = chd69 == "Yes" ~ dibpat*age,
    "family" = binomial(link = "logit")
)

chd_glm_contrasts |>
  parameters() |>
  print_md()
```

	Log-				
Parameter	Odds	SE	95% CI	${f z}$	p
(Intercept)	-5.50	0.67	(-6.83, -4.19)	-8.18	< .001
dibpat (Type B)	-0.30	1.18	(-2.63, 2.02)	-0.26	0.797
age	0.07	0.01	(0.05, 0.10)	5.24	< .001
dibpat (Type B) $\times$	-0.01	0.02	(-0.06, 0.04)	-0.42	0.674
age					

Compare with what we had before:

```
chd_glm_strat |>
  parameters() |>
  print_md()
```

	Log-				
Parameter	Odds	SE	95% CI	${f z}$	p
dibpat (Type A)	-5.50	0.67	(-6.83, -4.19)	-8.18	< .001
dibpat (Type B)	-5.80	0.98	(-7.73, -3.90)	-5.95	< .001
dibpat (Type A) $\times$	0.07	0.01	(0.05, 0.10)	5.24	< .001
age					
dibpat (Type B) $\times$	0.06	0.02	(0.02, 0.10)	3.01	0.003
age					

Exercise 3.12. If I give you model 1, how would you get the coefficients of model 2?

# 3.5. Fitting logistic regression models

### 3.5.1.

In general, the estimating equation  $\ell'(\beta; \mathbf{x}) = 0$  cannot be solved analytically.

Instead, we have to use a variant of the Newton-Raphson method, which was discussed briefly in Epi 203. We won't go over it in this class; if you need to learn it, see Dobson and Barnett (2018), Chapter 4.

For now, all you need to know is that we make an iterative series of guesses, and each guess helps us make the next guess better (higher log-likelihood).

You can see some information about this process like so:

```
options(digits = 8)
temp =
  wcgs |>
```

```
glm(
    control = glm.control(trace = TRUE),
    "data" = _,
    "formula" = chd69 == "Yes" ~ dibpat*age,
    "family" = binomial(link = "logit")
)

#> Deviance = 1775.7899 Iterations - 1
#> Deviance = 1708.5396 Iterations - 2
#> Deviance = 1704.0434 Iterations - 3
#> Deviance = 1703.9833 Iterations - 4
#> Deviance = 1703.9832 Iterations - 5
#> Deviance = 1703.9832 Iterations - 6
```

After each iteration of the fitting procedure, the deviance  $(2(\ell_{\text{full}} - \ell(\hat{\beta})))$  is printed. You can see that the algorithm took six iterations to converge to a solution where the likelihood wasn't changing much anymore.

# 3.6. Model comparisons for logistic models

#### 3.6.1. Deviance test

We can compare the maximized log-likelihood of our model,  $\ell(\hat{\beta}; \mathbf{x})$ , versus the log-likelihood of the full model (aka saturated model aka maximal model),  $\ell_{\text{full}}$ , which has one parameter per covariate pattern. With enough data,  $2(\ell_{\text{full}} - \ell(\hat{\beta}; \mathbf{x})) \dot{\sim} \chi^2(N-p)$ , where N is the number of distinct covariate patterns and p is the number of  $\beta$  parameters in our model. A significant p-value for this **deviance** statistic indicates that there's some detectable pattern in the data that our model isn't flexible enough to catch.

#### Caution

The deviance statistic needs to have a large amount of data for each covariate pattern for the  $\chi^2$  approximation to hold. A guideline from Dobson is that if there are q distinct covariate patterns  $x_1...,x_q$ , with  $n_1, ..., n_q$  observations per pattern, then the expected frequencies  $n_k \cdot \pi(x_k)$  should be at least 1 for every pattern  $k \in 1:q$ .

If you have covariates measured on a continuous scale, you may not be able to use the deviance tests to assess goodness of fit.

#### 3.6.2. Hosmer-Lemeshow test

If our covariate patterns produce groups that are too small, a reasonable solution is to make bigger groups by merging some of the covariate-pattern groups together.

Hosmer and Lemeshow (1980) proposed that we group the patterns by their predicted probabilities according to the model of interest. For example, you could group all of the observations with predicted probabilities of 10% or less together, then group the observations with 11%-20% probability together, and so on; q = 10 categories in all.

Then we can construct a statistic

$$X^2 = \sum_{c=1}^g \frac{(o_c - e_c)^2}{e_c}$$

where  $o_c$  is the number of events observed in group c, and  $e_c$  is the number of events expected in group c (based on the sum of the fitted values  $\hat{\pi}_i$  for observations in group c).

If each group has enough observations in it, you can compare  $X^2$  to a  $\chi^2$ distribution; by simulation, the degrees of freedom has been found to be approximately q-2.

For our CHD model, this procedure would be:

```
wcgs =
  wcgs |>
  mutate(
    pred_probs_glm1 = chd_glm_strat |> fitted(),
    pred_prob_cats1 =
      pred_probs_glm1 |>
      cut(breaks = seq(0, 1, by = .1),
          include.lowest = TRUE))
HL_table =
  wcgs |>
  summarize(
    .by = pred_prob_cats1,
    n = n(),
   o = sum(chd69 == "Yes"),
    e = sum(pred_probs_glm1)
  )
HL_table |> pander()
```

pred_prob_cats1	n	0	e
(0.1, 0.2]	785	116	108
(0.2, 0.3]	64	12	13.77
[0,0.1]	2305	129	135.2

```
pull(`X^2`)
print(X2)
#> [1] 1.1102871

pval1 = pchisq(X2, lower = FALSE, df = nrow(HL_table) - 2)
```

Our statistic is  $X^2 = 1.11028711$ ;  $p(\chi^2(1) > 1.11028711) = 0.29201955$ , which is our p-value for detecting a lack of goodness of fit.

Unfortunately that grouping plan left us with just three categories with any observations, so instead of grouping by 10% increments of predicted probability, typically analysts use deciles of the predicted probabilities:

```
wcgs =
  wcgs |>
  mutate(
    pred_probs_glm1 = chd_glm_strat |> fitted(),
    pred_prob_cats1 =
      pred_probs_glm1 |>
      cut(breaks = quantile(pred_probs_glm1, seq(0, 1, by = .1)),
          include.lowest = TRUE))
HL_table =
  wcgs |>
  summarize(
    .by = pred_prob_cats1,
    n = n(),
    o = sum(chd69 == "Yes"),
    e = sum(pred_probs_glm1)
  )
HL_table |> pander()
```

pred_prob_cats1	n	О	e
(0.114, 0.147]	275	48	36.81
(0.147, 0.222]	314	51	57.19
(0.0774, 0.0942]	371	27	32.56
(0.0942, 0.114]	282	30	29.89
(0.0633, 0.069]	237	17	15.97
(0.069, 0.0774]	306	20	22.95
(0.0487, 0.0633]	413	27	24.1
(0.0409, 0.0487]	310	14	14.15
[0.0322, 0.0363]	407	16	13.91
(0.0363, 0.0409]	239	7	9.48

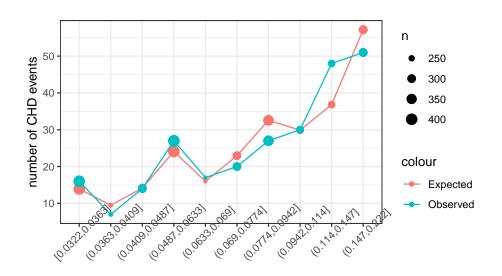
Now we have more evenly split categories. The p-value is 0.56041994, still not significant.

Graphically, we have compared:

```
HL_plot =
HL_table |>
ggplot(aes(x = pred_prob_cats1)) +
```

```
geom_line(aes(y = e, x = pred_prob_cats1, group = "Expected", col = "Expected")) +
geom_point(aes(y = e, size = n, col = "Expected")) +
geom_point(aes(y = o, size = n, col = "Observed")) +
geom_line(aes(y = o, col = "Observed", group = "Observed")) +
scale_size(range = c(1,4)) +
theme_bw() +
ylab("number of CHD events") +
theme(axis.text.x = element_text(angle = 45))
```

### print(HL\_plot)



pred\_prob\_cats1

### 3.6.3. Comparing models

• AIC =  $-2 * \ell(\hat{\theta}) + 2 * p$  [lower is better]

- BIC =  $-2 * \ell(\hat{\theta}) + p * \log(n)$  [lower is better]
- likelihood ratio [higher is better]

# 3.7. Residual-based diagnostics

### 3.7.1. Logistic regression residuals only work for grouped data

Residuals only work if there is more than one observation for most covariate patterns.

Here we will create the grouped-data version of our CHD model from the WCGS study:

```
wcgs_grouped =
wcgs |>
summarize(
    .by = c(dibpat, age),
    n = n(),
    chd = sum(chd69 == "Yes"),
        '!chd` = sum(chd69 == "No")
)

chd_glm_strat_grouped = glm(
    "formula" = cbind(chd, `!chd`) ~ dibpat + dibpat:age - 1,
    "data" = wcgs_grouped,
    "family" = binomial(link = "logit")
)

chd_glm_strat_grouped |> parameters() |> print_md()
```

	Log-				
Parameter	Odds	SE	95% CI	${f z}$	p
dibpat (Type A)	-5.50	0.67	(-6.83, -4.19)	-8.18	< .001
dibpat (Type B)	-5.80	0.98	(-7.73, -3.90)	-5.95	< .001
dibpat (Type A) $\times$	0.07	0.01	(0.05, 0.10)	5.24	< .001
age					
dibpat (Type B) $\times$	0.06	0.02	(0.02, 0.10)	3.01	0.003
age					

## 3.7.2. (Response) residuals

$$e_k \stackrel{\mathrm{def}}{=} \bar{y}_k - \hat{\pi}(x_k)$$

(k indexes the covariate patterns)

We can graph these residuals  $e_k$  against the fitted values  $\hat{\pi}(x_k)$ :

```
wcgs_grouped =
  wcgs_grouped |>
mutate(
  fitted = chd_glm_strat_grouped |> fitted(),
  fitted_logit = fitted |> logit(),
  response_resids =
      chd_glm_strat_grouped |> resid(type = "response")
)

wcgs_response_resid_plot =
  wcgs_grouped |>
  ggplot(
  mapping = aes(
      x = fitted,
      y = response_resids
```

```
)
) +
geom_point(
  aes(col = dibpat)
) +
geom_hline(yintercept = 0) +
geom_smooth(
  se = TRUE,
  method.args = list(
    span=2/3,
    degree=1,
    family="symmetric",
    iterations=3),
  method = stats::loess)
```

① Don't worry about these options for now; I chose them to match autoplot() as closely as I can. plot.glm and autoplot use stats::lowess instead of stats::lowess; stats::lowess is older, hard to use with geom\_smooth, and hard to match exactly with stats::lowess; see https://support.bioconductor.org/p/2323/.]

```
wcgs_response_resid_plot |> print()
```



We can see a slight fan-shape here: observations on the right have larger variance (as expected since  $var(\bar{y}) = \pi(1-\pi)/n$  is maximized when  $\pi = 0.5$ ).

# 3.7.3. Pearson residuals

The fan-shape in the response residuals plot isn't necessarily a concern here, since we haven't made an assumption of constant residual variance, as we did for linear regression.

However, we might want to divide by the standard error in order to make the graph easier to interpret. Here's one way to do that:

The Pearson (chi-squared) residual for covariate pattern k is:

$$X_k = \frac{\bar{y}_k - \hat{\pi}_k}{\sqrt{\hat{\pi}_k (1 - \hat{\pi}_k)/n_k}}$$

where

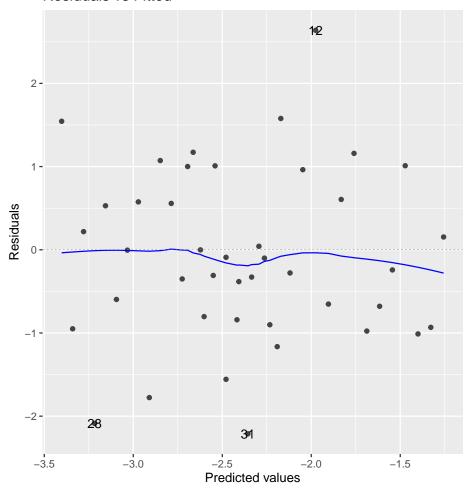
$$\begin{split} \hat{\pi}_k & \stackrel{\text{def}}{=} \hat{\pi}(x_k) \\ & \stackrel{\text{def}}{=} \hat{P}(Y = 1 | X = x_k) \\ & \stackrel{\text{def}}{=} \operatorname{expit}(x_i' \hat{\beta}) \\ & \stackrel{\text{def}}{=} \operatorname{expit}(\hat{\beta}_0 + \sum_{i=1}^p \hat{\beta}_j x_{ij}) \end{split}$$

Let's take a look at the Pearson residuals for our CHD model from the WCGS data (graphed against the fitted values on the logit scale):

```
library(ggfortify)
```

autoplot(chd\_glm\_strat\_grouped, which = 1, ncol = 1) |> print()

# Residuals vs Fitted



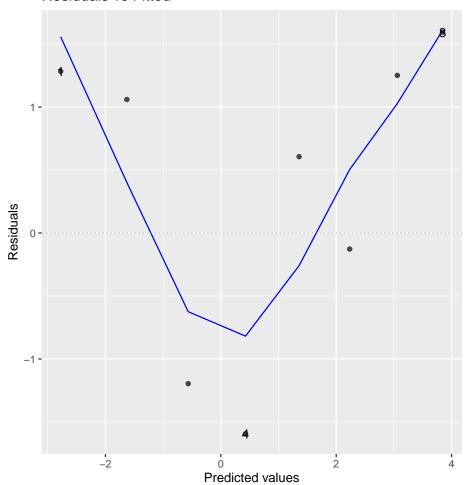
The fan-shape is gone, and these residuals don't show any obvious signs of model fit issues.

# 3.7.3.1. Pearson residuals plot for beetles data

If we create the same plot for the beetles model, we see some strong evidence of a lack of fit:

autoplot(beetles\_glm\_grouped, which = 1, ncol = 1) |> print()

# Residuals vs Fitted



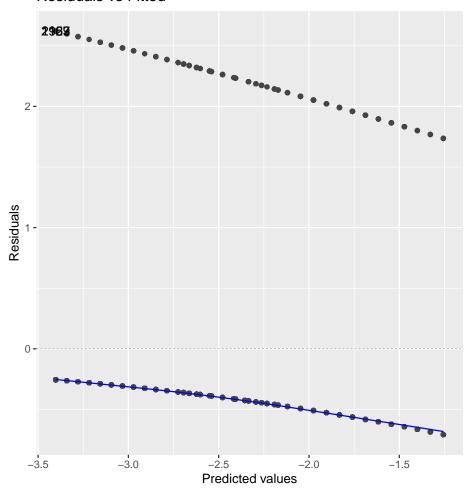
# 3.7.3.2. Pearson residuals with individual (ungrouped) data

What happens if we try to compute residuals without grouping the data by covariate pattern?

# library(ggfortify)

# autoplot(chd\_glm\_strat, which = 1, ncol = 1) |> print()

# Residuals vs Fitted



Meaningless.

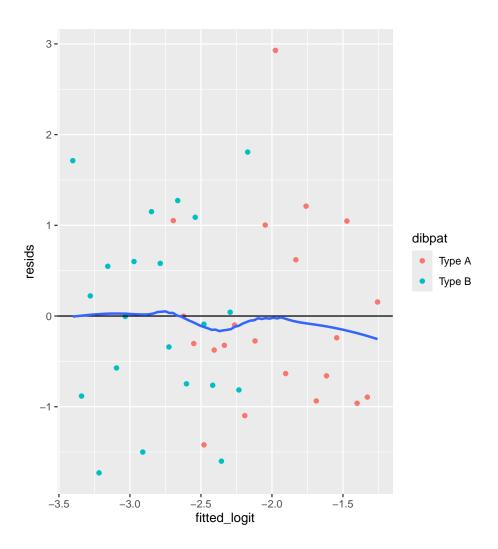
# 3.7.3.3. Residuals plot by hand (optional section)

If you want to check your understanding of what these residual plots are, try building them yourself:

```
wcgs_grouped =
 wcgs_grouped |>
 mutate(
   fitted = chd_glm_strat_grouped |> fitted(),
   fitted_logit = fitted |> logit(),
    resids = chd_glm_strat_grouped |> resid(type = "pearson")
wcgs_resid_plot1 =
 wcgs_grouped |>
 ggplot(
   mapping = aes(
     x = fitted_logit,
     y = resids
    )
  ) +
 geom_point(
   aes(col = dibpat)
  geom_hline(yintercept = 0) +
  geom_smooth(se = FALSE,
              method.args = list(
                span=2/3,
```

```
degree=1,
    family="symmetric",
    iterations=3,
    surface="direct"
    # span = 2/3,
    # iterations = 3
    ),
    method = stats::loess)

# plot.glm and autoplot use stats::lowess, which is hard to use with
# geom_smooth and hard to match exactly;
# see https://support.bioconductor.org/p/2323/
```



# 3.7.4. Pearson chi-squared goodness of fit test

The Pearson chi-squared goodness of fit statistic is:

$$X^2 = \sum_{k=1}^{m} X_k^2$$

Under the null hypothesis that the model in question is correct (i.e., sufficiently complex),  $X^2 \sim \chi^2(N-p)$ .

```
X = chd_glm_strat_grouped |>
  resid(type = "pearson")

chisq_stat = sum(X^2)

pval = pchisq(
  chisq_stat,
  lower = FALSE,
  df = length(X) - length(coef(chd_glm_strat_grouped)))
```

For our CHD model, the p-value for this test is 0.26523556; no significant evidence of a lack of fit at the 0.05 level.

### 3.7.4.1. Standardized Pearson residuals

Especially for small data sets, we might want to adjust our residuals for leverage (since outliers in X add extra variance to the residuals):

$$r_{P_k} = \frac{X_k}{\sqrt{1-h_k}}$$

where  $h_k$  is the leverage of  $X_k$ . The functions autoplot() and plot.lm() use these for some of their graphs.

# 3.7.5. Deviance residuals

For large sample sizes, the Pearson and deviance residuals will be approximately the same. For small sample sizes, the deviance residuals from covariate patterns with small sample sizes can be unreliable (high variance).

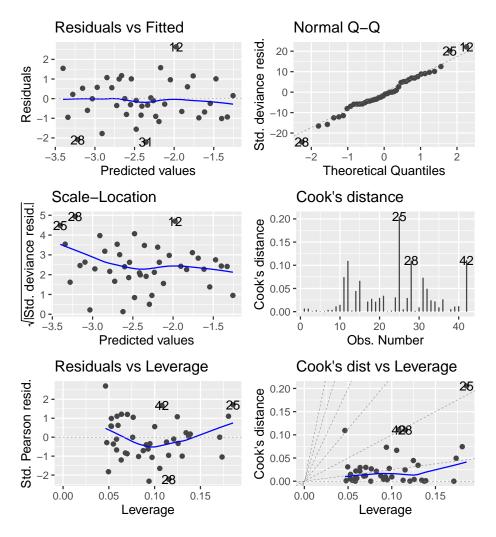
$$d_k = \mathrm{sign}(y_k - n_k \hat{\pi}_k) \left\{ \sqrt{2[\ell_{\mathrm{full}}(x_k) - \ell(\hat{\beta}; x_k)]} \right\}$$

# 3.7.5.1. Standardized deviance residuals

$$r_{D_k} = \frac{d_k}{\sqrt{1-h_k}}$$

# 3.7.6. Diagnostic plots

Let's take a look at the full set of autoplot() diagnostics now for our CHD model:



Things look pretty good here. The QQ plot is still usable; with large samples; the residuals should be approximately Gaussian.

# 3.7.6.1. Beetles

Let's look at the beetles model diagnostic plots for comparison:

```
beetles_glm_grouped |> autoplot(which = 1:6) |> print()
```



Hard to tell much from so little data, but there might be some issues here.

# 3.8. Odds Ratios vs Probability (Risk) Ratios

# 3.8.0.1. Case 1: rare events

For rare events, odds ratios and probability (a.k.a. risk, a.k.a. prevalence) ratios will be close:

```
\pi_1 = .01~\pi_2 = .02
```

```
pi1 = .01
pi2 = .02
pi2/pi1
#> [1] 2
odds(pi2)/odds(pi1)
#> [1] 2.0204082
```

# 3.8.0.2. Case 2: frequent events

```
\pi_1 = .4 \ \pi_2 = .5
```

For more frequently-occurring outcomes, this won't be the case:

```
pi1 = .4
pi2 = .5
pi2/pi1
#> [1] 1.25
odds(pi2)/odds(pi1)
#> [1] 1.5
```

If you want risk ratios, you can sometimes get them by changing the link function:

```
data(anthers, package = "dobson")
anthers.sum<-aggregate(
   anthers[c("n","y")],
   by=anthers[c("storage")],FUN=sum)

anthers_glm_log = glm(
   formula = cbind(y,n-y)~storage,
   data=anthers.sum,
   family=binomial(link="log"))

anthers_glm_log |> parameters() |> print_md()
```

Parameter	Log-Risk	SE	95% CI	${f z}$	р
(Intercept) storage	-0.80 0.17		(-1.04, -0.58) (0.02, 0.31)		< .001 0.021

Now  $\exp \{\beta\}$  gives us risk ratios instead of odds ratios:

```
anthers_glm_log |> parameters(exponentiate = TRUE) |> print_md()
```

Parameter	Risk Ratio	SE	95% CI	Z	p
(Intercept)	0.45	0.05	(0.35, 0.56)	-6.81	< .001
storage	1.18	0.09	(1.03, 1.36)	2.31	0.021

Let's compare this model with a logistic model:

```
anthers_glm_logit = glm(
  formula = cbind(y, n - y) ~ storage,
```

```
data = anthers.sum,
  family = binomial(link = "logit"))
anthers_glm_logit |> parameters(exponentiate = TRUE) |> print_md()
```

Parameter	Odds Ratio	SE	95% CI	Z	p
(Intercept) storage	0.76 1.49		(0.45, 1.27) (1.06, 2.10)		

[to add: fitted plots on each outcome scale]

When I try to use link ="log" in practice, I often get errors about not finding good starting values for the estimation procedure. This is likely because the model is producing fitted probabilities greater than 1.

When this happens, you can try to fit Poisson regression models instead (we will see those soon!). But then the outcome distribution isn't quite right, and you won't get warnings about fitted probabilities greater than 1. In my opinion, the Poisson model for binary outcomes is confusing and not very appealing.

Poisson regression and variations

# Acknowledgements

This content is adapted from:

- Dobson and Barnett (2018), Chapter 9
- Vittinghoff et al. (2012), Chapter 8

# **Configuring R**

Functions from these packages will be used throughout this document:

```
library(pander) # format tables for markdown
library(ggplot2) # graphics
library(ggeasy) # help with graphics
library(dplyr) # manipulate data
library(haven) # import Stata files
library(knitr) # format R output for markdown
library(tidyr) # Tools to help to create tidy data
```

```
library(plotly) # interactive graphics
library(dobson) # datasets from Dobson and Barnett 2018
library(parameters) # format model output tables for markdown
library(conflicted) # check for conflicting function definitions
```

Here are some R settings I use in this document:

```
rm(list = ls()) # delete any data that's already loaded into R
knitr::opts_chunk$set(message = FALSE)
pander::panderOptions("table.emphasize.rownames", FALSE)
options('digits' = 4)
```

# 4.1. Introduction

# 4.1.1. Examples of count outcomes

- Cyclones per season
- Seconds of tooth-brushing per session (if rounded)
- Infections per person-year
- Visits to ER per person-month
- Car accidents per 1000 miles driven

# Note

In many count outcomes, there is some sense of "exposure magnitude" or "duration of observation": person-year, time at risk, session, miles driven, etc.

# 4.1.2. Poisson distribution

$$P(Y=y) = \frac{\mu^y e^{-\mu}}{y!}$$

# 4.1.2.1. Properties

- $\bullet \quad \mathbb{E}[Y] = \mu$
- $Var[Y] = \mu$

# 4.1.3. Accounting for exposure

If the exposures/observation durations, denoted T=t, are not all equal, we model

$$\mu = \lambda t$$

 $\lambda$  is interpreted as the "expected event rate per unit of exposure"; that is,

$$\lambda = \frac{\mathbb{E}[Y|T=t]}{t}$$

# ! Important

The exposure magnitude, T, is *similar* to a covariate in linear or logistic regression. However, there is an important difference: in count regression, **there is no intercept corresponding to**  $\mathbb{E}[Y|T=0]$ . In other words, this model assumes that if there is no exposure, there can't be any events.

# 4.1.4. Adding covariates

With covariates,  $\lambda$  becomes a function of the covariates  $\tilde{X} = (X_1, \dots, X_n)$ , with a log  $\{\}$  link function (and thus an exp  $\{\}$  inverse-link). That is:

$$\begin{split} \mathbb{E}[Y|\tilde{X} = \tilde{x}, T = t] &= \mu(\tilde{x}, t) \\ \mu(\tilde{x}, t) &= \lambda(\tilde{x}) \cdot t \\ \lambda(\tilde{x}) &= \exp\left\{\eta(\tilde{x})\right\} \\ \eta(\tilde{x}) &= \tilde{x}'\tilde{\beta} = \beta_0 + \beta_1 x_1 + \dots + \beta_p x_p \end{split}$$

Therefore,

$$\begin{split} \log\left\{\left\{\mathbb{E}[Y|\tilde{X}=\tilde{x},T=t]\right\}\right\} &= \log\left\{\left\{\mu(\tilde{x})\right\}\right\} \\ &= \log\left\{\left\{\lambda(\tilde{x})\cdot t\right\}\right\} \\ &= \log\left\{\lambda(\tilde{x})\right\} + \log\left\{t\right\} \\ &= \log\left\{\exp\left\{\eta(\tilde{x})\right\}\right\} + \log\left\{t\right\} \\ &= \eta(\tilde{x}) + \log\left\{t\right\} \\ &= \tilde{x}'\tilde{\beta} + \log\left\{t\right\} \\ &= (\beta_0 + \beta_1 x_1 + \dots + \beta_p x_p) + \log\left\{t\right\} \end{split}$$

In contrast with the Xs, T enters this expression with a  $\log\{\}$  transformation and without a corresponding  $\beta$  coefficient.

# Note

Terms that enter the linear component of a model without a coefficient, such as  $\log \{t\}$  here, are called **offsets**.

# 4.1.5. Rate ratios

Differences on the log-rate scale become ratios on the rate scale.

 $\P$  Tip  $\exp\left\{a-b\right\} = \frac{\exp\left\{a\right\}}{\exp\left\{b\right\}}$ 

Therefore, according to this model, differences of  $\delta$  in covariate  $x_j$  correspond to rate ratios of  $\exp\left\{\beta_j \cdot \delta\right\}$ .

That is, letting  $\tilde{X}_{-j}$  denote vector  $\tilde{X}$  with element j removed:

$$\begin{split} &\left\{ \begin{array}{l} \log \left\{ \mathbb{E}[Y|\mathbf{X}_j = a, \tilde{X}_{-j} = \tilde{x}_{-j}, T = t] \right\} \\ -\log \left\{ \mathbb{E}[Y|\mathbf{X}_j = b, \tilde{X}_{-j} = \tilde{x}_{-j}, T = t] \right\} \end{array} \right\} \\ &= \left\{ \begin{array}{l} \log \left\{ t \right\} + \beta_0 + \beta_1 x_1 + \ldots + \beta_j (a) + \ldots + \beta_p x_p \\ -\log \left\{ t \right\} + \beta_0 + \beta_1 x_1 + \ldots + \beta_j (b) + \ldots + \beta_p x_p \end{array} \right\} \\ &= \beta_j (a - b) \end{split}$$

And accordingly,

$$\frac{\mathbb{E}[Y|\boldsymbol{X}_j=a,\tilde{X}_{-j}=\tilde{x}_{-j},T=t]}{\mathbb{E}[Y|\boldsymbol{X}_j=b,\tilde{X}_{-j}=\tilde{x}_{-j},T=t]}=\exp\left\{\beta_j(a-b)\right\}$$

# 4.2. Inference for count regression models

# 4.2.1. Confidence intervals for regression coefficients and rate ratios

As usual:

$$\beta \in \left[\hat{\beta} \pm z_{1 - \frac{\alpha}{2}} \cdot \hat{\operatorname{se}}\left(\hat{\beta}\right)\right]$$

Rate ratios: exponentiate CI endpoints

$$\exp\left\{\beta\right\} \in \left[\exp\left\{\hat{\beta} \pm z_{1-\frac{\alpha}{2}} \cdot \hat{\operatorname{se}}\left(\hat{\beta}\right)\right\}\right]$$

# 4.2.2. Hypothesis tests for regression coefficients

$$t = \frac{\hat{\beta} - \beta_0}{\hat{\operatorname{se}}\left(\hat{\beta}\right)}$$

Compare t or |t| to the tails of the standard Gaussian distribution, according to the null hypothesis.

# 4.2.3. Comparing nested models

log(likelihood ratio) tests, as usual.

# 4.3. Prediction

$$\begin{split} \hat{y} &\stackrel{\text{def}}{=} \hat{\mathbb{E}}[Y|\tilde{X} = \tilde{x}, T = t] \\ &= \hat{\mu}(\tilde{x}, t) \\ &= \hat{\lambda}(\tilde{x}) \cdot t \\ &= \exp\left\{\hat{\eta}(\tilde{x})\right\} \cdot t \\ &= \exp\left\{\tilde{x}'\hat{\beta}\right\} \cdot t \end{split}$$

# 4.4. Diagnostics

# 4.4.1. Residuals

# 4.4.1.1. Observation residuals

$$e \stackrel{\text{def}}{=} y - \hat{y}$$

# 4.4.1.2. Pearson residuals

$$r = \frac{e}{\hat{\operatorname{se}}\left(e\right)} \approx \frac{e}{\sqrt{\hat{y}}}$$

# 4.4.1.3. Standardized Pearson residuals

$$r_p = \frac{r}{\sqrt{1-h}}$$

where h is the "leverage" (which we will continue to leave undefined).

# 4.4.1.4. Deviance residuals

$$d_k = \mathrm{sign}(y - \hat{y}) \left\{ \sqrt{2[\ell_{\mathrm{full}}(y) - \ell(\hat{\beta}; y)]} \right\}$$

# Note

$$\operatorname{sign}(x) \stackrel{\text{def}}{=} \frac{x}{|x|}$$

In other words:

- $\operatorname{sign}(x) = -1 \text{ if } x < 0$
- $\operatorname{sign}(x) = 0$  if x = 0
- $\operatorname{sign}(x) = 1 \text{ if } x > 0$

# 4.5. Zero-inflation

# 4.5.1. Models for zero-inflated counts

We assume a latent (unobserved) binary variable, Z, which we model using logistic regression:

$$P(Z=1|X=x)=\pi(x)=\operatorname{expit}(\gamma_0+\gamma_1x_1+\ldots)$$

According to this model, if Z = 1, then Y will always be zero, regardless of X and T:

$$P(Y = 0|Z = 1, X = x, T = t) = 1$$

Otherwise (if Z=0), Y will have a Poisson distribution, conditional on X and T, as above.

Even though we never observe Z, we can estimate the parameters  $\gamma_0$ - $\gamma_p$ , via maximum likelihood:

$$P(Y = y|X = x, T = t) = P(Y = y, Z = 1|...) + P(Y = y, Z = 0|...)$$

(by the Law of Total Probability)

where

$$P(Y = y, Z = z | ...) = P(Y = y | Z = z, ...) P(Z = z | ...)$$

# 4.5.1.1. Exercise

Expand P(Y=0|X=x,T=t), P(Y=1|X=x,T=t) and P(Y=y|X=x,T=t) into expressions involving P(Z=1|X=x,T=t) and P(Y=y|Z=0,X=x,T=t).

# 4.5.1.2. Exercise

Derive the expected value and variance of Y, conditional on X and T, as functions of P(Z=1|X=x,T=t) and  $\mathbb{E}[Y|Z=0,X=x,T=t]$ .

# 4.6. Over-dispersion

# 4.6.1. Negative binomial models

The Poisson distribution model **forces** the variance to equal the mean. In practice, many count distributions will have a variance substantially larger than the mean (or occasionally smaller).

When we encounter this, we can try to reduce the residual variance by adding more covariates. However, there are also alternatives to the Poisson model.

Most notably, the negative binomial model:

$$P(Y = y) = \frac{\mu^y}{y!} \cdot \frac{\Gamma(\rho + y)}{\Gamma(\rho) \cdot (\rho + \mu)^y} \cdot \left(1 + \frac{\mu}{\rho}\right)^{-\rho}$$

where  $\rho$  is an overdispersion parameter and  $\Gamma(x)=(x-1)!$  for integers x.

You don't need to memorize or understand this expression, but as  $\rho \to \infty$ , the second term converges to 1 and the third term converges to  $\exp\{-\mu\}$ , which brings us back to the Poisson distribution.

For this distribution,  $\mathbb{E}[Y] = \mu$  and  $\operatorname{Var}(Y) = \mu + \frac{\mu^2}{\rho} > \mu$ .

We can still model  $\mu$  as a function of X and T as before, and we can combine this model with zero-inflation by using it in place of the Poisson distribution for P(Y = y | Z = 0, X = x, T = t).

# 4.6.2. Quasipoisson

An alternative to Negative binomial is the "quasipoisson" distribution. I've never used it, but it seems to be a method-of-moments type approach rather than maximum likelihood. It models the variance as  $\text{Var}(Y) = \mu\theta$ , and estimates  $\theta$  accordingly.

See ?quasipoisson in R for more.

# Part II. Time to Event Models

In many health sciences applications, binary outcomes are *incompletely observed*. For example, if we are studying whether cancer patients experience a relapse after a initial remission, we may may not be able to follow patients to the end of their lives; instead, we may only know whether each patient has relapsed before the end of the study. If a patient has not relapsed by that point, we might not know if they will relapse at some other date or if they will stay cancer-free for the rest of their lives. <sup>1</sup> Their recurrence status at end-of-life is *missing data*. If some study participants withdraw from a study before the end date in the study design, there will be even more missing data. All of this missing data will make logistic regression difficult for this type of data.

However, these outcome observations are not *entirely* missing. We know that those patients stayed relapse free *at least* until the time point when we last saw them. If we also know the *time-to-event* for the participants who did experience events while under study, we can analyze *time-to-event-or-study-exit*, combined with the indicator of which of these two cases occurred, using *survival analysis*. The survival analysis framework is the subject of the rest of these course notes.

<sup>&</sup>lt;sup>1</sup>Binary outcomes are typically defined for a specific time-point. It is important to clearly define whether we are interested in outcome status at end of study, at end of life, or at some other time.

# Configuring R

Functions from these packages will be used throughout this document:

```
library(pander) # format tables for markdown
library(ggplot2) # graphics
library(ggeasy) # help with graphics
library(scales) # scales formatting
library(dplyr) # manipulate data
library(haven) # import Stata files
library(knitr) # format R output for markdown
library(tidyr) # Tools to help to create tidy data
library(plotly) # interactive graphics
library(dobson) # datasets from Dobson and Barnett 2018
library(parameters) # format model output tables for markdown
library(conflicted) # check for conflicting function definitions
```

Here are some R settings I use in this document:

```
rm(list = ls()) # delete any data that's already loaded into R
knitr::opts_chunk$set(message = FALSE)
pander::panderOptions("table.emphasize.rownames", FALSE)
pander::panderOptions("table.split.table", Inf)
conflicts_prefer(dplyr::filter) # use the `filter()` function from dplyr() by defaul
options('digits' = 4)
```

# 5.1. Overview

# 5.1.1. Time-to-event outcomes

**Survival analysis** is a framework for modeling *time-to-event* outcomes. It is used in:

- clinical trials, where the event is often death or recurrence of disease.
- engineering reliability analysis, where the event is failure of a device or system.
- insurance, particularly life insurance, where the event is death.

# Note

The term *Survival analysis* is a bit misleading. Survival outcomes can sometimes be analyzed using binomial models (logistic regression). *Time-to-event models* might be a better name.

# 5.2. Time-to-event outcome distributions

# 5.2.1. Distributions of Time-to-Event Data

- The distribution of event times is asymmetric and can be long-tailed, and starts at 0 (that is, P(T < 0) = 0).
- The base distribution is not normal, but exponential.
- There are usually **censored** observations, which are ones in which the failure time is not observed.
- Often, these are **right-censored**, meaning that we know that the event occurred after some known time t, but we don't know the actual event time, as when a patient is still alive at the end of the study.

- Observations can also be **left-censored**, meaning we know the event has already happened at time t, or **interval-censored**, meaning that we only know that the event happened between times  $t_1$  and  $t_2$ .
- Analysis is difficult if censoring is associated with treatment.

# 5.2.2. Right Censoring

- Patients are in a clinical trial for cancer, some on a new treatment and some on standard of care.
- Some patients in each group have died by the end of the study. We know the survival time (measured for example from time of diagnosis—each person on their own clock).
- Patients still alive at the end of the study are right censored.
- Patients who are lost to follow-up or withdraw from the study may be right-censored.

# 5.2.3. Left and Interval Censoring

- An individual tests positive for HIV.
- If the event is infection with HIV, then we only know that it has occurred before the testing time t, so this is left censored.
- If an individual has a negative HIV test at time  $t_1$  and a positive HIV test at time  $t_2$ , then the infection event is interval censored.

# 5.3. Distribution functions for time-to-event variables

# 5.3.1. The Probability Density Function (PDF)

For a time-to-event variable T with a continuous distribution, the **probability density function** is defined as usual:

$$f(t) \stackrel{\text{def}}{=} p(t) \stackrel{\text{def}}{=} p(T=t)$$

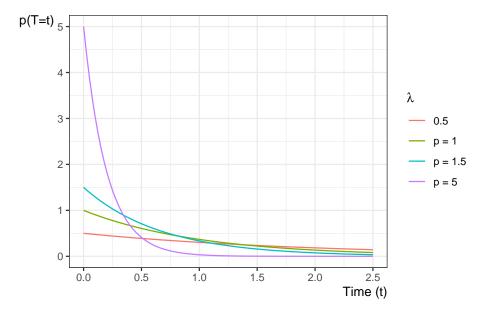
Typically, this density is assumed to be 0 for all t < 0; that is,  $f(t) = 0, \forall t < 0$ . In other words, the range of T is typically  $[0, \infty)$ .

**Example 5.1** (exponential distribution). Recall from Epi 202: the pdf of the exponential distribution family of models is:

$$p(T=t) = \mathbb{1}_{t \geq 0} \cdot \lambda \mathrm{e}^{-\lambda t}$$

where  $\lambda > 0$ .

Here are some examples of exponential pdfs:



# 5.3.2. The Cumulative Distribution Function (CDF)

The **cumulative distribution function** is defined as:

$$F(t) \stackrel{\text{def}}{=} \Pr(T \le t)$$
 
$$= \int_{u=0}^{t} f(u) du$$

**Example 5.2** (exponential distribution). Recall from Epi 202: the cdf of the exponential distribution family of models is:

$$P(T \le t) = \mathbb{1}_{t > 0} \cdot (1 - e^{-\lambda t})$$

where  $\lambda > 0$ .

Here are some examples of exponential cdfs:



# 5.3.3. The Survival Function

For survival data, a more important quantity is the **survival function**:

$$S(t) \stackrel{\text{def}}{=} \Pr(T > t)$$
 
$$= \int_{u=t}^{\infty} p(u) du$$
 
$$= 1 - F(t)$$

The survival function S(t) is the probability that the event time is later than t. If the event in a clinical trial is death, then S(t) is the expected fraction of the original population at time 0 who have survived up to time t and are still alive at time t; that is, if  $X_t$  represents survival status at time t, with  $X_t = 1$  denoting alive at time t and  $X_t = 0$  denoting deceased at time t, then:

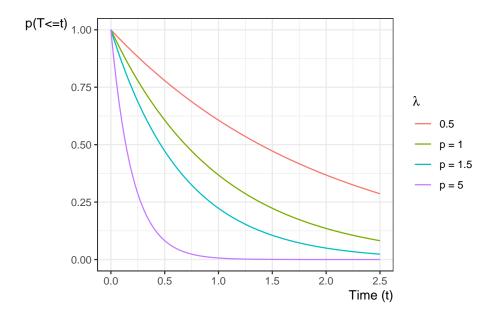
$$S(t) = \mathbb{E}\left[X_t\right]$$

**Example 5.3** (exponential distribution). Since S(t) = 1 - F(t), the survival function of the exponential distribution family of models is:

$$P(T > t) = \begin{cases} e^{-\lambda t}, t \ge 0\\ 1, t \le 0 \end{cases}$$

where  $\lambda > 0$ .

Here are some examples of exponential pdfs:



# 5.3.4. The Hazard Function

Another important quantity is the **hazard function**:

**Definition 5.1** (Hazard function). The hazard function for a random variable T at value t is the conditional density of T at t, given  $T \ge t$ ; that is:

$$h(t) \stackrel{\text{def}}{=} p(T = t | T \ge t)$$

If T represents the time at which an event occurs, then h(t) is the probability that the event occurs at time t, given that it has not occurred prior to time t.

The hazard function has an important relationship to the density and survival functions, which we can use to derive the hazard function for a given probability distribution.

Theorem 5.1.

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

Proof.

Lemma 5.1 (Joint probability of a variable with itself).

$$p(T = t, T \ge t) = p(T = t)$$

*Proof.* Recall from Epi 202: if A and B are statistical events and  $A \subseteq B$ , then p(A,B)=p(A). In particular,  $\{T=t\}\subseteq \{T\geq t\}$ , so  $p(T=t,T\geq t)=p(T=t)$ .

Hence:

$$\begin{split} h(t) &= p(T=t|T \geq t) \\ &= \frac{p(T=t, T \geq t)}{p(T \geq t)} \\ &= \frac{p(T=t)}{p(T \geq t)} \\ &= \frac{f(t)}{S(t)} \end{split}$$

**Example 5.4** (exponential distribution). The hazard function of the exponential distribution family of models is:

$$\begin{split} P(T=t|T\geq t) &= \frac{f(t)}{S(t)} \\ &= \frac{\mathbb{1}_{t\geq 0} \cdot \lambda \mathrm{e}^{-\lambda t}}{\mathrm{e}^{-\lambda t}} \\ &= \mathbb{1}_{t\geq 0} \cdot \lambda \end{split}$$

Figure 5.1 shows some examples of exponential hazard functions:

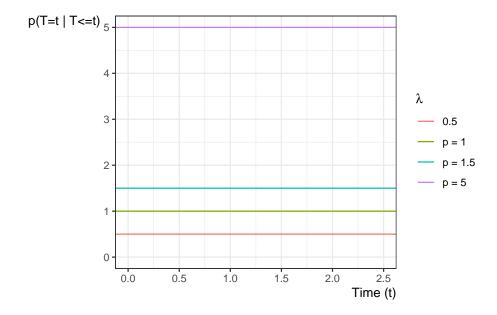


Figure 5.1.: Examples of hazard functions for exponential distributions

We can also view the hazard function as the derivative of the negative of the logarithm of the survival function:

Theorem 5.2.

$$h(t) = \frac{d}{dt} \left\{ -\log \left\{ S(t) \right\} \right\}$$

Proof.

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

$$= \frac{-S'(t)}{S(t)}$$

$$= -\frac{S'(t)}{S(t)}$$

$$= -\frac{d}{dt} \log \{S(t)\}$$

$$= \frac{d}{dt} \{-\log \{S(t)\}\}$$

5.3.5. The Cumulative Hazard Function

Since  $h(t) = \frac{d}{dt} \{-\log \{S(t)\}\}\$  (see Theorem 5.2), we also have:

Corollary 5.1.

$$S(t) = exp\left\{-\int_{u=0}^{t} h(u)du\right\}$$
 (5.1)

The integral in Equation 5.1 is important enough to have its own name: cumulative hazard.

**Definition 5.2** (cumulative hazard). The **cumulative hazard function** H(t) is defined as:

$$H(t) \stackrel{\mathrm{def}}{=} \int_{u=0}^{t} h(u) du$$

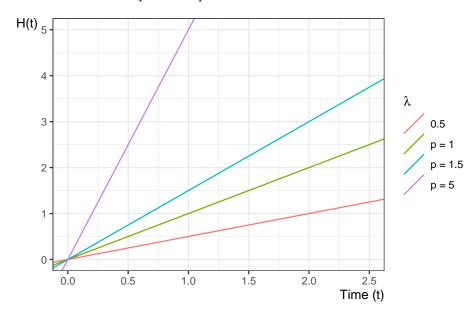
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As we will see below, H(t) is tractable to estimate, and we can then derive an estimate of the hazard function using an approximate derivative of the estimated cumulative hazard.

**Example 5.5.** The cumulative hazard function of the exponential distribution family of models is:

$$H(t)=\mathbb{1}_{t\geq 0}\cdot \lambda t$$

Here are some examples of exponential cumulative hazard functions:



# 5.3.6. Some Key Mathematical Relationships among Survival Concepts

Diagram:

$$h(t) \xrightarrow{\int_{u=0}^{t} h(u)du} H(t) \xrightarrow{\exp\{-H(t)\}} S(t) \xrightarrow{1-S(t)} F(t)$$

$$h(t) \xleftarrow{\frac{d}{dt} H(t)} H(t) \xleftarrow{-\log\{S(t)\}} S(t) \xleftarrow{1-F(t)} F(t)$$

Identities:

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

$$= \exp \{-H(t)\}$$

$$S'(t) = -f(t)$$

$$H(t) = -\log \{S(t)\}$$

$$H'(t) = h(t)$$

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

$$= -\frac{d}{dt} \log \{S(t)\}$$

$$f(t) = h(t) \cdot S(t)$$

Some proofs (others left as exercises):

$$S'(t) = \frac{d}{dt}(1 - F(t))$$

$$= -F'(t)$$

$$= -f(t)$$

$$\frac{d}{dt}\log\{S(t)\} = \frac{S'(t)}{S(t)}$$

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

$$= -h(t)$$

$$H(t) \stackrel{\text{def}}{=} \int_{u=0}^{t} h(u)du$$

$$= \int_{0}^{t} -\frac{d}{du} \log \{S(u)\} du$$

$$= \left[ -\log \{S(u)\} \right]_{u=0}^{u=t}$$

$$= \left[ \log \{S(u)\} \right]_{u=t}^{u=0}$$

$$= \log \{S(0)\} - \log \{S(t)\}$$

$$= \log \{1\} - \log \{S(t)\}$$

$$= 0 - \log \{S(t)\}$$

$$= -\log \{S(t)\}$$

Equivalently:

$$S(t) = \exp\left\{-H(t)\right\}$$

# 5.3.6.1. Example: Time to death the US in 2004

# Daily hazard rates for US Females in 2004

The first day is the most dangerous:



Figure 5.2.: Daily Hazard Rates in 2004 for US Females

Daily hazard rates for US Males and Females in 2004

Exercise: hypothesize why these curves differ where they do?



Figure 5.3.: Daily Hazard Rates in 2004 for US Males and Females 1-40  $\,$ 

# Survival curve for US females

Exercise: compare and contrast this curve with the corresponding hazard curve.



Figure 5.4.: Survival Curve in 2004 for US Females

# 5.3.6.2. Likelihood with censoring \*

# Note

This subsection was not presented in class in 2023; it is not necessary to understand for the qualifying exam.

If an event time T is observed exactly as T=t, then the likelihood of that observation is just its probability density function:

$$\begin{split} \mathcal{L}(t) &= p(T = t) \\ &\stackrel{\text{def}}{=} f_T(t) \\ &= h_T(t) S_T(t) \\ \ell(t) \stackrel{\text{def}}{=} \log \left\{ \mathcal{L}(t) \right\} \\ &= \log \left\{ h_T(t) S_T(t) \right\} \\ &= \log \left\{ h_T(t) \right\} + \log \left\{ S_T(t) \right\} \\ &= \log \left\{ h_T(t) \right\} - H_T(t) \end{split}$$

If instead the event time T is censored and only known to be after time y, then the likelihood of that censored observation is instead the survival function evaluated at the censoring time:

$$\begin{split} \mathcal{L}(y) &= p_T(T > y) \\ &\stackrel{\text{def}}{=} S_T(y) \\ \ell(y) &\stackrel{\text{def}}{=} \log \left\{ \mathcal{L}(y) \right\} \\ &= \log \left\{ S(y) \right\} \\ &= -H(y) \end{split}$$

What's written above is incomplete. We also observed whether or not the observation was censored. Let C denote the time when censoring would occur (if the event did not occur first); let  $f_C(y)$  and  $S_C(y)$  be the corresponding density and survival functions for the censoring event.

Let Y denote the time when observation ended (either by censoring or by the event of interest occurring), and let D be an indicator variable for the event occurring at Y (so D=0 represents a censored observation and D=1 represents an uncensored observation). In other words, let  $Y \stackrel{\text{def}}{=} \min(T,C)$  and  $D \stackrel{\text{def}}{=} \mathbb{1}\{T \le C\}$ .

Then the complete likelihood of the observed data (Y, D) is:

$$\mathcal{L}(y,d) = p(Y = y, D = d)$$

$$= [p(T = y, C > y)]^{d} \cdot [p(T > y, C = y)]^{1-d}$$

Typically, survival analyses assume that C and T are mutually independent; this assumption is called "non-informative" censoring.

Then the joint likelihood p(Y,D) factors into the product p(Y),p(D), and the likelihood reduces to:

$$\begin{split} \mathcal{L}(y,d) &= \left[ p(T=y,C>y) \right]^d \cdot \left[ p(T>y,C=y) \right]^{1-d} \\ &= \left[ p(T=y)p(C>y) \right]^d \cdot \left[ p(T>y)p(C=y) \right]^{1-d} \\ &= \left[ f_T(y)S_C(y) \right]^d \cdot \left[ S(y)f_C(y) \right]^{1-d} \\ &= \left[ f_T(y)^d S_C(y)^d \right] \cdot \left[ S_T(y)^{1-d} f_C(y)^{1-d} \right] \\ &= (f_T(y)^d \cdot S_T(y)^{1-d}) \cdot (f_C(y)^{1-d} \cdot S_C(y)^d) \end{split}$$

The corresponding log-likelihood is:

$$\begin{split} \ell(y,d) &= \log \left\{ \mathcal{L}(y,d) \right\} \\ &= \log \left\{ \left( f_T(y)^d \cdot S_T(y)^{1-d} \right) \cdot \left( f_C(y)^{1-d} \cdot S_C(y)^d \right) \right\} \\ &= \log \left\{ f_T(y)^d \cdot S_T(y)^{1-d} \right\} + \log \left\{ f_C(y)^{1-d} \cdot S_C(y)^d \right\} \end{split}$$

Let

- $\theta_T$  represent the parameters of  $p_T(t)$ ,
- $\theta_C$  represent the parameters of  $p_C(c)$ ,
- $\theta = (\theta_T, \theta_C)$  be the combined vector of all parameters.

Then corresponding score function is:

$$\begin{split} \ell'(y,d) &= \frac{d}{d\theta} \left[ \log \left\{ f_T(y)^d \cdot S_T(y)^{1-d} \right\} + \log \left\{ f_C(y)^{1-d} \cdot S_C(y)^d \right\} \right] \\ &= \left( \frac{d}{d\theta} \log \left\{ f_T(y)^d \cdot S_T(y)^{1-d} \right\} \right) + \left( \frac{d}{d\theta} \log \left\{ f_C(y)^{1-d} \cdot S_C(y)^d \right\} \right) \end{split}$$

As long as  $\theta_C$  and  $\theta_T$  don't share any parameters, then if censoring is non-informative, the partial derivative with respect to  $\theta_T$  is:

$$\begin{split} \ell_{\theta_T}'(y,d) &\stackrel{\text{def}}{=} \frac{d}{d\theta_T} \ell(y,d) \\ &= \left( \frac{d}{d\theta_T} \log \left\{ f_T(y)^d \cdot S_T(y)^{1-d} \right\} \right) + \left( \frac{d}{d\theta_T} \log \left\{ f_C(y)^{1-d} \cdot S_C(y)^d \right\} \right) \\ &= \left( \frac{d}{d\theta_T} \log \left\{ f_T(y)^d \cdot S_T(y)^{1-d} \right\} \right) + 0 \\ &= \frac{d}{d\theta_T} \log \left\{ f_T(y)^d \cdot S_T(y)^{1-d} \right\} \end{split}$$

Thus, the MLE for  $\theta_T$  won't depend on  $\theta_C$ , and we can ignore the distribution of C when estimating the parameters of  $f_T(t) = p(T=t)$ .

Then:

$$\begin{split} \mathcal{L}(y,d) &= f_T(y)^d \cdot S_T(y)^{1-d} \\ &= (h_T(y)^d S_T(y)^d) \cdot S_T(y)^{1-d} \\ &= h_T(y)^d \cdot S_T(y)^d \cdot S_T(y)^{1-d} \\ &= h_T(y)^d \cdot S_T(y) \\ &= S_T(y) \cdot h_T(y)^d \end{split}$$

That is, if the event occurred at time y (i.e., if d = 1), then the likelihood of (Y, D) = (y, d) is equal to the hazard function at y times the survival

function at y. Otherwise, the likelihood is equal to just the survival function at y.

The corresponding log-likelihood is:

$$\begin{split} \ell(y,d) &= \log \left\{ \mathcal{L}(y,d) \right\} \\ &= \log \left\{ S_T(y) \cdot h_T(y)^d \right\} \\ &= \log \left\{ S_T(y) \right\} + \log \left\{ h_T(y)^d \right\} \\ &= \log \left\{ S_T(y) \right\} + d \cdot \log \left\{ h_T(y) \right\} \\ &= -H_T(y) + d \cdot \log \left\{ h_T(y) \right\} \end{split}$$

In other words, the log-likelihood contribution from a single observation (Y, D) = (y, d) is equal to the negative cumulative hazard at y, plus the log of the hazard at y if the event occurred at time y.

Note

End of extra section.

# 5.4. Parametric Models for Time-to-Event Outcomes

# 5.4.1. Exponential Distribution

- The exponential distribution is the base distribution for survival analysis.
- The distribution has a constant hazard  $\lambda$
- The mean survival time is  $\lambda^{-1}$

### 5.4.1.1. Mathematical details of exponential distribution

$$\begin{split} f(t) &= \lambda \mathrm{e}^{-\lambda t} \\ E(t) &= \lambda^{-1} \\ Var(t) &= \lambda^{-2} \\ F(t) &= 1 - \mathrm{e}^{-\lambda x} \\ S(t) &= \mathrm{e}^{-\lambda x} \\ \ln(S(t)) &= -\lambda x \\ h(t) &= -\frac{f(t)}{S(t)} = -\frac{\lambda \mathrm{e}^{-\lambda t}}{\mathrm{e}^{-\lambda t}} = \lambda \end{split}$$

### **5.4.1.2.** Estimation of $\lambda$

- Suppose we have m exponential survival times of  $t_1, t_2, \ldots, t_m$  and k right-censored values at  $u_1, u_2, \ldots, u_k$ .
- A survival time of  $t_i = 10$  means that subject i died at time 10. A right-censored time  $u_i = 10$  means that at time 10, subject i was still alive and that we have no further follow-up.
- For the moment we will assume that the survival distribution is exponential and that all the subjects have the same parameter  $\lambda$ .

We have m exponential survival times of  $t_1,t_2,\ldots,t_m$  and k right-censored values at  $u_1,u_2,\ldots,u_k$ . The log-likelihood of an observed survival time  $t_i$  is

$$\log \left\{ \lambda e^{-\lambda t_i} \right\} = \log \left\{ \lambda \right\} - \lambda t_i$$

and the likelihood of a censored value is the probability of that outcome (survival greater than  $u_i$ ) so the log-likelihood is

$$\log\left\{\lambda \mathbf{e}^{u_j}\right\} = -\lambda u_j.$$

Let 
$$T = \sum t_i$$
 and  $U = \sum u_i$ . Then:

$$\begin{split} \ell(\lambda) &= \sum_{i=1}^m (\ln \lambda - \lambda t_i) + \sum_{j=1}^k (-\lambda u_j) \\ &= m \ln \lambda - (T+U)\lambda \\ \ell'(\lambda) &= m\lambda^{-1} - (T+U) \\ \hat{\lambda} &= \frac{m}{T+U} \\ \ell'' &= -m/\lambda^2 \\ &< 0 \\ \hat{E}[T] &= \hat{\lambda}^{-1} \\ &= \frac{T+U}{m} \end{split}$$

### 5.4.1.3. Fisher Information and Standard Error

$$\begin{split} E[-\ell''] &= m/\lambda^2 \\ \operatorname{Var}\left(\hat{\lambda}\right) &\approx \left(E[-\ell'']\right)^{-1} \\ &= \lambda^2/m \\ \operatorname{SE}\left(\hat{\lambda}\right) &= \sqrt{\operatorname{Var}\left(\hat{\lambda}\right)} \\ &\approx \lambda/\sqrt{m} \end{split}$$

 $\hat{\lambda}$  depends on the censoring times of the censored observations, but  $\text{Var}(\hat{\lambda})$  only depends on the number of uncensored observations, m, and not on the number of censored observations (k).

#### 5.4.1.4. Other Parametric Survival Distributions

• Any density on  $[0, \infty)$  can be a survival distribution, but the most useful ones are all skew right.

- The commonest generalization of the exponential is the Weibull.
- Other common choices are the gamma, log-normal, log-logistic, Gompertz, inverse Gaussian, and Pareto.
- Most of what we do going forward is non-parametric or semiparametric, but sometimes these parametric distributions provide a useful approach.

#### 5.4.2. Weibull Distribution

$$\begin{split} p(t) &= \alpha \lambda x^{\alpha-1} \mathrm{e}^{-\lambda x^{\alpha}} \\ h(t) &= \alpha \lambda x^{\alpha-1} \\ S(t) &= \mathrm{e}^{-\lambda x^{\alpha}} \\ E(T) &= \Gamma(1+1/\alpha) \cdot \lambda^{-1/\alpha} \end{split}$$

When  $\alpha = 1$  this is the exponential. When  $\alpha > 1$  the hazard is increasing and when  $\alpha < 1$  the hazard is decreasing. This provides more flexibility than the exponential.

We will see more of this distribution later.

# 5.5. Nonparametric Survival Analysis

### 5.5.1. Basic ideas

- Mostly, we work without a parametric model.
- The first task is to estimate a survival function from data listing survival times, and censoring times for censored data.
- For example one patient may have relapsed at 10 months. Another might have been followed for 32 months without a relapse having occurred (censored).

• The minimum information we need for each patient is a time and a censoring variable which is 1 if the event occurred at the indicated time and 0 if this is a censoring time.

# 5.6. Example: clinical trial for pediatric acute leukemia

# 5.6.1. Overview of study

This is from a clinical trial in 1963 for 6-MP treatment vs. placebo for Acute Leukemia in 42 children.

- Pairs of children:
  - matched by remission status at the time of treatment (remstat:
     1 = partial, 2 = complete)
  - randomized to 6-MP (exit times in t2) or placebo (exit times in t1)
- Followed until relapse or end of study.
- All of the placebo group relapsed, but some of the 6-MP group were censored (which means they were still in remission); indicated by relapse variable (0 = censored, 1 = relapse).
- 6-MP = 6-Mercaptopurine (Purinethol) is an anti-cancer ("antineoplastic" or "cytotoxic") chemotherapy drug used currently for Acute lymphoblastic leukemia (ALL). It is classified as an antimetabolite.

# 5.6.2. Study design

Clinical trial in 1963 for 6-MP treatment vs. placebo for Acute Leukemia in 42 children. Pairs of children matched by remission status at the time of treatment (1 = partial or 2 = complete) and randomized to 6-MP or placebo. Followed until relapse or end of study. All of the placebo group relapsed, but some of the 6-MP group were censored.

```
library(KMsurv)
data(drug6mp)
drug6mp |> tibble() |> print()
```

```
# A tibble: 21 x 5
    pair remstat
                       t1
                              t2 relapse
   <int>
                                   <int>
            <int> <int> <int>
 1
                 1
                        1
                                        1
                              10
 2
        2
                 2
                       22
                               7
 3
        3
                 2
                        3
                              32
 4
        4
                 2
                       12
                              23
                                        1
        5
                 2
 5
                        8
                              22
                                        1
 6
        6
                 1
                       17
                               6
                                        1
 7
        7
                 2
                        2
                              16
                                        1
                 2
 8
                                        0
        8
                       11
                              34
 9
        9
                 2
                        8
                              32
                                        0
                 2
                                        0
10
      10
                       12
                              25
# i 11 more rows
```

# 5.6.3. Data documentation for drug6mp

```
library(printr) # inserts help-file output into markdown output
library(KMsurv)
?drug6mp
```

```
data from Section 1.2
```

# Description:

The 'drug6mp' data frame has 21 rows and 5 columns.

#### Format:

```
This data frame contains the following columns:
```

pair pair number

remstat Remission status at randomization (1=partial, 2=complete)

t1 Time to relapse for placebo patients, months

t2 Time to relapse for 6-MP patients, months

relapse Relapse indicator (0=censored, 1=relapse) for 6-MP patients

# 5.6.4. Descriptive Statistics

- The average time in each group is not useful. Some of the 6-MP patients have not relapsed at the time recorded, while all of the placebo patients have relapsed.
- The median time is not really useful either because so many of the 6-MP patients have not relapsed (12/21).
- Both are biased down in the 6-MP group. Remember that lower times are worse since they indicate sooner recurrence.
- We can compute the average hazard rate, which is the estimate of the exponential parameter: number of relapses divided by the sum of the times.

- For the placebo, that is just the reciprocal of the mean time = 1/8.667 = 0.115.
- For the 6-MP group this is 9/359 = 0.025
- The estimated average hazard in the placebo group is 4.6 times as large (if the hazard is constant over time).

# 5.7. The Kaplan-Meier Product Limit Estimator

- The estimated survival function for the placebo patients is easy to compute. For any time t in months, S(t) is the fraction of patients with times greater than t.
- For the 6-MP patients, we cannot ignore the censored data because we know that the time to relapse is greater than the censoring time.
- For any time t in months, we know that 6-MP patients with times greater than t have not relapsed, and those with relapse time less than t have relapsed, but we don't know if patients with censored time less than t have relapsed or not.
- The procedure we usually use is the Kaplan-Meier product-limit estimator of the survival function.
- The Kaplan-Meier estimator is a step function (like the empirical cdf), which changes value only at the event times, not at the censoring times.
- At each event time t, we compute the at-risk group size Y, which is all those observations whose event time or censoring time is at least t.
- If d of the observations have an event time (not a censoring time) of t, then the group of survivors immediately following time t is reduced by the fraction

$$\frac{Y-d}{Y} = 1 - \frac{d}{Y}$$

If the event times are  $t_i$  with events per time of  $d_i$   $(1 \le i \le k)$ , then

$$\hat{S}(t) = \prod_{t_i < t} [1 - d_i/Y_i]$$

where  $Y_i$  is the set of observations whose time (event or censored) is  $\geq t_i$ , the group at risk at time  $t_i$ .

If there are no censored data, and there are n data points, then just after (say) the third event time

$$\begin{split} \hat{S}(t) &= \prod_{t_i < t} [1 - d_i / Y_i] \\ &= [\frac{n - d_1}{n}] [\frac{n - d_1 - d_2}{n - d_1}] [\frac{n - d_1 - d_2 - d_3}{n - d_1 - d_2}] \\ &= \frac{n - d_1 - d_2 - d_3}{n} \\ &= 1 - \frac{d_1 + d_2 + d_3}{n} \\ &= 1 - \hat{F}(t) \end{split}$$

where  $\hat{F}(t)$  is the usual empirical CDF estimate.

# 5.7.1. Kaplan-Meier curve for drug6mp data

Here is the Kaplan-Meier estimated survival curve for the patients who received 6-MP in the drug6mp dataset (we will see code to produce figures like this one shortly):

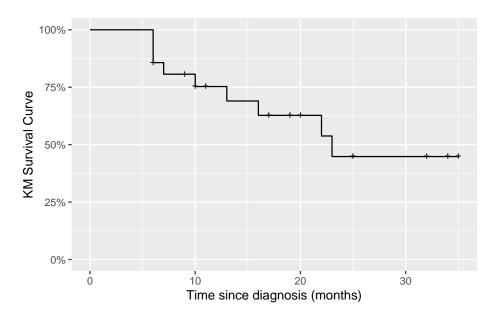


Figure 5.5.: Kaplan-Meier Survival Curve for 6-MP Patients

# 5.7.2. Kaplan-Meier calculations

Let's compute these estimates and build the chart by hand:

```
library(KMsurv)
library(dplyr)
data(drug6mp)

drug6mp.v2 =
   drug6mp |>
   as_tibble() |>
   mutate(
   remstat = remstat |>
```

```
case_match(
       1 ~ "partial",
        2 ~ "complete"
    # renaming to "outcome" while relabeling is just a style choice:
    outcome = relapse |>
      case_match(
      0 ~ "censored",
        1 ~ "relapsed"
  )
km.6mp =
 drug6mp.v2 |>
  summarize(
    .by = t2,
   Relapses = sum(outcome == "relapsed"),
   Censored = sum(outcome == "censored")) |>
  # here we add a start time row, so the graph starts at time 0:
  bind_rows(
   tibble(
     t2 = 0,
     Relapses = 0,
      Censored = 0)
  ) |>
  # sort in time order:
  arrange(t2) |>
 mutate(
   Exiting = Relapses + Censored,
   `Study Size` = sum(Exiting),
   Exited = cumsum(Exiting) |> dplyr::lag(default = 0),
   `At Risk` = `Study Size` - Exited,
   Hazard = Relapses / `At Risk`,
```

										KM
								KM		Sur-
				Study		$\operatorname{At}$		Fac-	Cumula	
t2	Rela	ps <b>&amp;</b> enso	or <b>Ec</b> kiti	·	Exit	eRisk	Haza	rdtor	Hazard	Curve
0	0	0	0	21	0	21	0	1	0	1
6	3	1	4	21	0	21	0.142	290.8571	0.1429	0.8571
7	1	0	1	21	4	17	0.058	8 <b>2</b> .9412	0.2017	0.8067
9	0	1	1	21	5	16	0	1	0.2017	0.8067
10	1	1	2	21	6	15	0.066	667.9333	0.2683	0.7529
11	0	1	1	21	8	13	0	1	0.2683	0.7529
13	1	0	1	21	9	12	0.083	3 <b>3</b> .9167	0.3517	0.6902
16	1	0	1	21	10	11	0.090	90.9091	0.4426	0.6275
17	0	1	1	21	11	10	0	1	0.4426	0.6275
19	0	1	1	21	12	9	0	1	0.4426	0.6275
20	0	1	1	21	13	8	0	1	0.4426	0.6275
22	1	0	1	21	14	7	0.142	290.8571	0.5854	0.5378
23	1	0	1	21	15	6	0.166	70.8333	0.7521	0.4482
25	0	1	1	21	16	5	0	1	0.7521	0.4482
32	0	2	2	21	17	4	0	1	0.7521	0.4482
34	0	1	1	21	19	2	0	1	0.7521	0.4482
35	0	1	1	21	20	1	0	1	0.7521	0.4482

# 5.7.2.1. Summary

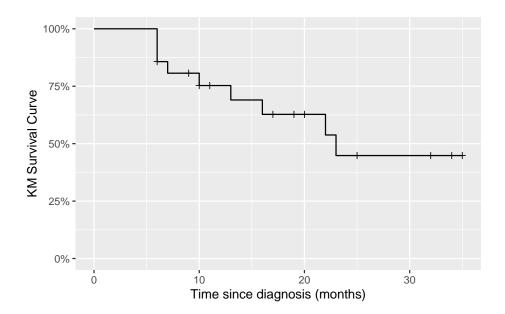
For the 6-MP patients at time 6 months, there are 21 patients at risk. At t = 6 there are 3 relapses and 1 censored observations.

The Kaplan-Meier factor is (21-3)/21 = 0.857. The number at risk for the next time (t=7) is 21-3-1=17.

At time 7 months, there are 17 patients at risk. At t=7 there is 1 relapse and 0 censored observations. The Kaplan-Meier factor is (17-1)/17=0.941. The Kaplan Meier estimate is  $0.857\times0.941=0.807$ . The number at risk for the next time (t=9) is 17-1=16.

Now, let's graph this estimated survival curve using ggplot():

```
library(ggplot2)
conflicts_prefer(dplyr::filter)
km.6mp |>
    ggplot(aes(x = t2, y = `KM Survival Curve`)) +
    geom_step() +
    geom_point(data = km.6mp |> filter(Censored > 0), shape = 3) +
    expand_limits(y = c(0,1), x = 0) +
    xlab('Time since diagnosis (months)') +
    ylab("KM Survival Curve") +
    scale_y_continuous(labels = scales::percent)
```



# 5.8. Using the survival package in R

We don't have to do these calculations by hand every time; the survival package and several others have functions available to automate many of these tasks (full list: https://cran.r-project.org/web/views/Survival.html).

# 5.8.1. The Surv function

To use the survival package, the first step is telling R how to combine the exit time and exit reason (censoring versus event) columns. The Surv() function accomplishes this task.

# 5.8.1.1. Example: Surv() with drug6mp data

```
library(survival)
drug6mp.v3 =
drug6mp.v2 |>
mutate(
surv2 = Surv(
time = t2,
event = (outcome == "relapsed")))

print(drug6mp.v3)
```

```
# A tibble: 21 x 7
    pair remstat
                      t1
                             t2 relapse outcome
                                                    surv2
   <int> <chr>
                   <int> <int>
                                  <int> <chr>
                                                   <Surv>
       1 partial
                       1
                             10
                                       1 relapsed
                                                      10
2
       2 complete
                      22
                              7
                                       1 relapsed
                                                       7
3
       3 complete
                       3
                             32
                                       0 censored
                                                      32+
4
       4 complete
                      12
                             23
                                       1 relapsed
                                                      23
5
                       8
                             22
                                       1 relapsed
                                                      22
       5 complete
6
       6 partial
                      17
                             6
                                       1 relapsed
                                                       6
 7
                       2
       7 complete
                                       1 relapsed
                                                      16
                             16
8
                             34
                                                      34+
       8 complete
                      11
                                       0 censored
9
       9 complete
                       8
                             32
                                       0 censored
                                                      32+
10
      10 complete
                      12
                             25
                                       0 censored
                                                      25+
# i 11 more rows
```

The output of Surv() is a vector of objects with class Surv. When we print this vector:

 observations where the event was observed are printed as the event time (for example, surv2 = 10 on line 1)

observations where the event was right-censored are printed as the censoring time with a plus sign (+; for example, surv2 = 32+ on line 3).

#### 5.8.2. The survfit function

Once we have constructed our Surv variable, we can calculate the Kaplan-Meier estimate of the survival curve using the survfit() function.

### Note

The documentation for ?survfit isn't too helpful; the survfit.formula documentation is better.

# 5.8.2.1. Example: survfit() with drug6mp data

Here we use survfit() to create a survfit object, which contains the Kaplan-Meier estimate:

```
drug6mp.km_model = survfit(
  formula = surv2 ~ 1,
  data = drug6mp.v3)
```

print.survfit() just gives some summary statistics:

summary.survfit() shows us the underlying Kaplan-Meier table:

```
summary(drug6mp.km_model)
```

Call: survfit(formula = surv2 ~ 1, data = drug6mp.v3)

time	n.risk	${\tt n.event}$	survival	std.err	lower	95% CI	upper	95% CI
6	21	3	0.857	0.0764		0.720		1.000
7	17	1	0.807	0.0869		0.653		0.996
10	15	1	0.753	0.0963		0.586		0.968
13	12	1	0.690	0.1068		0.510		0.935
16	11	1	0.627	0.1141		0.439		0.896
22	7	1	0.538	0.1282		0.337		0.858
23	6	1	0.448	0.1346		0.249		0.807

summary.survfit() shows us the underlying Kaplan-Meier table:

```
summary(drug6mp.km_model)
```

```
Call: survfit(formula = surv2 ~ 1, data = drug6mp.v3)
```

time	n.risk	${\tt n.event}$	survival	${\tt std.err}$	lower	95% CI	upper	95% CI
6	21	3	0.857	0.0764		0.720		1.000
7	17	1	0.807	0.0869		0.653		0.996
10	15	1	0.753	0.0963		0.586		0.968
13	12	1	0.690	0.1068		0.510		0.935
16	11	1	0.627	0.1141		0.439		0.896
22	7	1	0.538	0.1282		0.337		0.858
23	6	1	0.448	0.1346		0.249		0.807

We can specify which time points we want using the times argument:

```
summary(
  drug6mp.km_model,
  times = c(0, drug6mp.v3$t2))
Call: survfit(formula = surv2 ~ 1, data = drug6mp.v3)
 time n.risk n.event survival std.err lower 95% CI upper 95% CI
    0
           21
                     0
                          1.000
                                  0.0000
                                                  1.000
                                                                1.000
    6
           21
                     3
                          0.857
                                                  0.720
                                                                1.000
                                  0.0764
    6
           21
                     0
                          0.857
                                  0.0764
                                                  0.720
                                                                1.000
    6
           21
                     0
                          0.857
                                  0.0764
                                                  0.720
                                                                1.000
    6
           21
                     0
                          0.857
                                  0.0764
                                                  0.720
                                                                1.000
    7
                     1
           17
                          0.807
                                  0.0869
                                                  0.653
                                                                0.996
    9
           16
                     0
                          0.807
                                  0.0869
                                                  0.653
                                                                0.996
   10
           15
                     1
                          0.753
                                  0.0963
                                                  0.586
                                                                0.968
   10
           15
                     0
                          0.753
                                  0.0963
                                                  0.586
                                                                0.968
   11
           13
                     0
                          0.753
                                  0.0963
                                                  0.586
                                                                0.968
   13
           12
                     1
                          0.690
                                  0.1068
                                                  0.510
                                                                0.935
   16
           11
                     1
                          0.627
                                  0.1141
                                                  0.439
                                                                0.896
   17
                     0
                          0.627
                                                                0.896
           10
                                  0.1141
                                                  0.439
   19
            9
                     0
                          0.627
                                  0.1141
                                                  0.439
                                                                0.896
   20
            8
                     0
                          0.627
                                  0.1141
                                                  0.439
                                                                0.896
            7
   22
                     1
                          0.538
                                  0.1282
                                                  0.337
                                                                0.858
   23
            6
                     1
                          0.448
                                  0.1346
                                                                0.807
                                                  0.249
   25
            5
                          0.448
                     0
                                  0.1346
                                                  0.249
                                                                0.807
   32
            4
                     0
                          0.448
                                  0.1346
                                                  0.249
                                                                0.807
   32
            4
                     0
                          0.448
                                  0.1346
                                                  0.249
                                                                0.807
            2
                          0.448
                                                                0.807
   34
                     0
                                  0.1346
                                                  0.249
   35
            1
                     0
                          0.448
                                  0.1346
                                                  0.249
                                                                0.807
```

?summary.survfit

Summary of a Survival Curve

### Description:

Returns a list containing the survival curve, confidence limits for the curve, and other information.

### Usage:

```
## S3 method for class 'survfit'
summary(object, times, censored=FALSE, scale=1,
   extend=FALSE, rmean=getOption('survfit.rmean'), ...)
```

### Arguments:

object: the result of a call to the 'survfit' function.

times: vector of times; the returned matrix will contain 1 row for each time. The vector will be sorted into increasing order; missing values are not allowed. If 'censored=T', the default 'times' vector contains all the unique times in 'fit', otherwise the default 'times' vector uses only the event (death) times.

censored: logical value: should the censoring times be included in the output? This is ignored if the 'times' argument is present.

scale: numeric value to rescale the survival time, e.g., if the
 input data to 'survfit' were in days, 'scale = 365.25' would
 scale the output to years.

extend: logical value: if TRUE, prints information for all specified 'times', even if there are no subjects left at the end of the specified 'times'. This is only used if the 'times' argument is present.

rmean: Show restricted mean: see 'print.survfit' for details
...: for future methods

# 5.8.3. Plotting estimated survival functions

We can plot survfit objects with plot(), autoplot(), or ggsurvplot():

```
library(ggfortify)
autoplot(drug6mp.km_model)
```

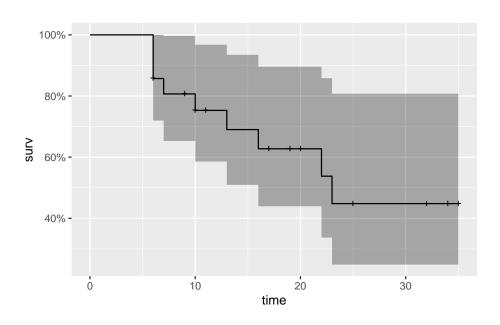


Figure 5.6.: Kaplan-Meier Survival Curve for 6-MP Patients

```
# not shown:
# plot(drug6mp.km_model)

# library(survminer)
# ggsurvplot(drug6mp.km_model)
```

# 5.8.3.1. quantiles of survival curve

We can extract quantiles with quantile():

```
drug6mp.km_model |>
quantile(p = c(.25, .5)) |>
as_tibble() |>
mutate(p = c(.25, .5)) |>
relocate(p, .before = everything())
```

р	quantile	lower	upper
0.25	13	6	NA
0.50	23	16	NA

# 5.8.4. Two-sample tests

# 5.8.4.1. The survdiff function

```
?survdiff
```

Test Survival Curve Differences

### Description:

Tests if there is a difference between two or more survival curves using the G-rho family of tests, or for a single curve against a known alternative.

### Usage:

survdiff(formula, data, subset, na.action, rho=0, timefix=TRUE)

### 5.8.4.2. Example: survdiff() with drug6mp data

Now we are going to compare the placebo and 6-MP data. We need to reshape the data to make it usable with the standard survival workflow:

```
library(survival)
drug6mp.v4 =
  drug6mp.v3 |>
  select(pair, remstat, t1, t2, outcome) |>
  # here we are going to change the data from a wide format to long:
  pivot_longer(
    cols = c(t1, t2),
   names_to = "treatment",
    values_to = "exit_time") |>
 mutate(
    treatment = treatment |>
      case_match(
        "t1" ~ "placebo",
        "t2" ~ "6-MP"
      ),
    outcome = if_else(
      treatment == "placebo",
```

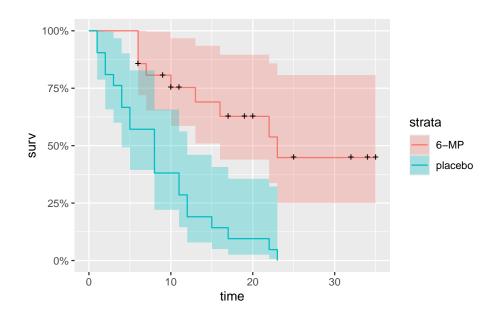
```
"relapsed",
  outcome
),
surv = Surv(
  time = exit_time,
  event = (outcome == "relapsed"))
)
```

Using this long data format, we can fit a Kaplan-Meier curve for each treatment group simultaneously:

```
drug6mp.km_model2 =
   survfit(
  formula = surv ~ treatment,
  data = drug6mp.v4)
```

We can plot the curves in the same graph:

```
drug6mp.km_model2 |> autoplot()
```



We can also perform something like a t-test, where the null hypothesis is that the curves are the same:

```
survdiff(
  formula = surv ~ treatment,
  data = drug6mp.v4)
```

Call:
survdiff(formula = surv ~ treatment, data = drug6mp.v4)

	N	Observed	Expected	$(0-E)^2/E$	$(0-E)^2/V$
treatment=6-MP	21	9	19.3	5.46	16.8
treatment=placebo	21	21	10.7	9.77	16.8

Chisq= 16.8 on 1 degrees of freedom, p= 4e-05

By default, survdiff() ignores any pairing, but we can use strata() to perform something similar to a paired t-test:

```
survdiff(
 formula = surv ~ treatment + strata(pair),
 data = drug6mp.v4)
Call:
survdiff(formula = surv ~ treatment + strata(pair), data = drug6mp.v4)
                   N Observed Expected (O-E)^2/E (O-E)^2/V
treatment=6-MP
                  21
                            9
                                   16.5
                                             3.41
                                                       10.7
treatment=placebo 21
                           21
                                   13.5
                                             4.17
                                                       10.7
```

Chisq= 10.7 on 1 degrees of freedom, p= 0.001

Interestingly, accounting for pairing reduces the significant of the difference.

## 5.9. Example: Bone Marrow Transplant Data

(Copelan et al., 1991)

- \* Treatment
  - allogeneic (from a donor) bone marrow transplant therapy
- \* Inclusion criteria
  - acute myeloid leukemia (AML)
  - acute lymphoblastic leukemia (ALL).

- \* Possible intermediate events
  - graft vs. host disease (GVHD): an immunological rejection response to the transplant
  - platelet recovery: a return of platelet count to normal levels.

One or the other, both in either order, or neither may occur.

#### End point events

- relapse of the disease
- death

Any or all of these events may be censored.

#### 5.9.1. KMsurv::bmt data in R

```
library(printr) # inserts help-file output into markdown output
library(KMsurv)
?bmt
```

data from Section 1.3

#### Description:

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

#### Format:

This data frame contains the following columns:

group Disease Group 1-ALL, 2-AML Low Risk, 3-AML High Risk

- t1 Time To Death Or On Study Time
- t2 Disease Free Survival Time (Time To Relapse, Death Or End Of Study)
- d1 Death Indicator 1-Dead 0-Alive
- d2 Relapse Indicator 1-Relapsed, 0-Disease Free
- d3 Disease Free Survival Indicator 1-Dead Or Relapsed, 0-Alive Disease Free)
- ta Time To Acute Graft-Versus-Host Disease
- da Acute GVHD Indicator 1-Developed Acute GVHD 0-Never Developed Acute GVHD)
- tc Time To Chronic Graft-Versus-Host Disease
- dc Chronic GVHD Indicator 1-Developed Chronic GVHD 0-Never Developed Chronic GVHD
- tp Time To Chronic Graft-Versus-Host Disease
- z1 Patient Age In Years
- z2 Donor Age In Years
- z3 Patient Sex: 1-Male, 0-Female

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

#### Source:

Klein and Moeschberger (1997) \_Survival Analysis Techniques for Censored and truncated data\_, Springer.

#### Examples:

data(bmt)

## 5.9.2. Analysis plan

- We concentrate for now on disease-free survival (t2 and d3) for the three risk groups, ALL, AML Low Risk, and AML High Risk.
- We will construct the Kaplan-Meier survival curves, compare them, and test for differences.
- We will construct the cumulative hazard curves and compare them.
- We will estimate the hazard functions, interpret, and compare them.

#### 5.9.3. Survival Function Estimate and Variance

$$\hat{S}(t) = \prod_{t_i < t} \left[ 1 - \frac{d_i}{Y_i} \right]$$

where  $Y_i$  is the group at risk at time  $t_i$ .

The estimated variance of  $\hat{S}(t)$  is (Greenwood's formula)

$$\hat{\mathrm{Var}}\left(\hat{S}(t)\right) = \hat{S}(t)^2 \sum_{t_i < t} \frac{d_i}{Y_i(Y_i - d_i)}$$

which we can use for confidence intervals for a survival function or a difference of survival functions.

#### Kaplan-Meier survival curves

```
library(KMsurv)
library(survival)
data(bmt)

bmt =
    bmt |>
    as_tibble() |>
    mutate(
        group =
            group |>
            factor(
                labels = c("ALL", "Low Risk AML", "High Risk AML")),
        surv = Surv(t2,d3))

km_model1 = survfit(
    formula = surv ~ group,
    data = bmt)
```

```
library(ggfortify)
autoplot(
   km_model1,
   conf.int = TRUE,
   ylab = "Pr(disease-free survival)",
   xlab = "Time since transplant (days)") +
   theme_bw() +
   theme(legend.position="bottom")
```

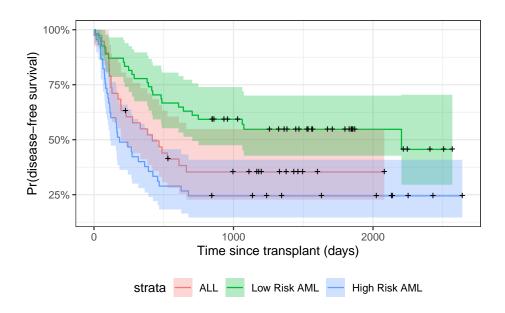


Figure 5.7.: Disease-Free Survival by Disease Group

## 5.9.3.1. Understanding Greenwood's formula (optional)

To see where Greenwood's formula comes from, let  $x_i = Y_i - d_i$ . We approximate the solution treating each time as independent, with  $Y_i$  fixed

and ignore randomness in times of failure and we treat  $x_i$  as independent binomials  $Bin(Y_i, p_i)$ . Letting S(t) be the "true" survival function

$$\begin{split} \hat{S}(t) &= \prod_{t_i < t} x_i / Y_i \\ S(t) &= \prod_{t_i < t} p_i \end{split}$$

$$\begin{split} \frac{\hat{S}(t)}{S(t)} &= \prod_{t_i < t} \frac{x_i}{p_i Y_i} = \prod_{t_i < t} \frac{\hat{p}_i}{p_i} \\ &= \prod_{t_i < t} \left(1 + \frac{\hat{p}_i - p_i}{p_i}\right) \\ &\approx 1 + \sum_{t_i < t} \frac{\hat{p}_i - p_i}{p_i} \end{split}$$

$$\begin{split} \operatorname{Var}\left(\frac{\hat{S}(t)}{S(t)}\right) &\approx \operatorname{Var}\left(1 + \sum_{t_i < t} \frac{\hat{p}_i - p_i}{p_i}\right) \\ &= \sum_{t_i < t} \frac{1}{p_i^2} \frac{p_i (1 - p_i)}{Y_i} \\ &= \sum_{t_i < t} \frac{(1 - p_i)}{p_i Y_i} \approx \sum_{t_i < t} \frac{(1 - x_i / Y_i)}{x_i} \\ &= \sum_{t_i < t} \frac{Y_i - x_i}{x_i Y_i} = \sum_{t_i < t} \frac{d_i}{Y_i (Y_i - d_i)} \end{split}$$
 
$$\operatorname{Var}\left(\hat{S}(t)\right) \approx \hat{S}(t)^2 \sum_{t_i < t} \frac{d_i}{Y_i (Y_i - d_i)} \end{split}$$

## 5.9.4. Test for differences among the disease groups

Here we compute a chi-square test for assocation between disease group (group) and disease-free survival:

#### Call:

survdiff(formula = surv ~ group, data = bmt)

	N	Observed	Expected	$(0-E)^2/E$	$(0-E)^2/V$
group=ALL	38	24	21.9	0.211	0.289
group=Low Risk AML	54	25	40.0	5.604	11.012
group=High Risk AML	45	34	21.2	7.756	10.529

Chisq= 13.8 on 2 degrees of freedom, p= 0.001

#### 5.9.5. Cumulative Hazard

$$\begin{split} h(t) &\stackrel{\text{def}}{=} P(T=t|T \geq t) \\ &= \frac{p(T=t)}{P(T \geq t)} \\ &= -\frac{d}{dt} \log \left\{ S(t) \right\} \end{split}$$

The cumulative hazard (or integrated hazard) function is

$$H(t) \stackrel{\text{def}}{=} \int_0^t h(t)dt$$

Since  $h(t) = -\frac{d}{dt} \mathrm{log} \left\{ S(t) \right\}$  as shown above, we have:

$$H(t) = -\log\{S\}(t)$$

So we can estimate H(t) as:

$$\begin{split} \hat{H}(t) &= -\mathrm{log}\left\{\hat{S}(t)\right\} \\ &= -\mathrm{log}\left\{\prod_{t_i < t} \left[1 - \frac{d_i}{Y_i}\right]\right\} \\ &= -\sum_{t_i < t} \mathrm{log}\left\{1 - \frac{d_i}{Y_i}\right\} \end{split}$$

This is the Kaplan-Meier (product-limit) estimate of cumulative hazard.

# 5.9.5.1. Example: Cumulative Hazard Curves for Bone-Marrow Transplant (bmt) data

```
autoplot(
  fun = "cumhaz",
  km_model1,
  conf.int = FALSE,
  ylab = "Cumulative hazard (disease-free survival)",
  xlab = "Time since transplant (days)") +
  theme_bw() +
  theme(legend.position="bottom")
```



Figure 5.8.: Disease-Free Cumulative Hazard by Disease Group

# 5.10. Nelson-Aalen Estimates of Cumulative Hazard and Survival

The point hazard at time  $t_i$  can be estimated by  $d_i/Y_i$ , which leads to the Nelson-Aalen estimator of the cumulative hazard:

$$\hat{H}_{NA}(t) \stackrel{\mathrm{def}}{=} \sum_{t_i < t} \frac{d_i}{Y_i}$$

The variance of this estimator is approximately:

$$\begin{split} \hat{\text{Var}}\left(\hat{H}_{NA}(t)\right) &= \sum_{t_i < t} \frac{(d_i/Y_i)(1 - d_i/Y_i)}{Y_i} \\ &\approx \sum_{t_i < t} \frac{d_i}{Y_i^2} \end{split}$$

Since  $S(t) = \exp\{-H(t)\}\$ , the Nelson-Aalen cumulative hazard estimate can be converted into an alternate estimate of the survival function:

$$\begin{split} \hat{S}_{NA}(t) &= \exp\left\{-\hat{H}_{NA}(t)\right\} \\ &= \exp\left\{-\sum_{t_i < t} \frac{d_i}{Y_i}\right\} \\ &= \prod_{t_i < t} \exp\left\{-\frac{d_i}{Y_i}\right\} \end{split}$$

Compare these with the corresponding Kaplan-Meier estimates:

$$\begin{split} \hat{H}_{KM}(t) &= -\sum_{t_i < t} \log \left\{ 1 - \frac{d_i}{Y_i} \right\} \\ \hat{S}_{KM}(t) &= \prod_{t_i < t} \left[ 1 - \frac{d_i}{Y_i} \right] \end{split}$$

The product limit estimate and the Nelson-Aalen estimate often do not differ by much. The latter is considered more accurate in small samples and also directly estimates the cumulative hazard. The "fleming-harrington" method for survfit() reduces to Nelson-Aalen when the data are unweighted. We can also estimate the cumulative hazard as the negative log of the KM survival function estimate.

## 5.10.1. Application to bmt dataset

```
na_fit = survfit(
  formula = surv ~ group,
  type = "fleming-harrington",
  data = bmt)

km_fit = survfit(
  formula = surv ~ group,
  type = "kaplan-meier",
  data = bmt)

km_and_na =
  bind_rows(
    .id = "model",
    "Kaplan-Meier" = km_fit |> fortify(surv.connect = TRUE),
    "Nelson-Aalen" = na_fit |> fortify(surv.connect = TRUE)
) |>
  as_tibble()
```

```
km_and_na |>
  ggplot(aes(x = time, y = surv, col = model)) +
  geom_step() +
  facet_grid(. ~ strata) +
  theme_bw() +
  ylab("S(t) = P(T>=t)") +
  xlab("Survival time (t, days)") +
  theme(legend.position = "bottom")
```



Figure 5.9.: Kaplan-Meier and Nelson-Aalen Survival Function Estimates, stratified by disease group

The Kaplan-Meier and Nelson-Aalen survival estimates are very similar for this dataset.

#### Configuring R

Functions from these packages will be used throughout this document:

```
library(pander) # format tables for markdown
library(ggplot2) # graphics
library(ggeasy) # help with graphics
library(dplyr) # manipulate data
library(haven) # import Stata files
library(knitr) # format R output for markdown
library(tidyr) # Tools to help to create tidy data
library(plotly) # interactive graphics
library(dobson) # datasets from Dobson and Barnett 2018
library(parameters) # format model output tables for markdown
library(conflicted) # check for conflicting function definitions
conflicts_prefer(dplyr::filter)
```

Here are some R settings I use in this document:

```
rm(list = ls()) # delete any data that's already loaded into R
knitr::opts_chunk$set(message = FALSE)
pander::panderOptions("table.emphasize.rownames", FALSE)
options('digits' = 4)
```

## 6.1. The proportional hazards model

## 6.1.1. Background on the Proportional Hazards Model

The exponential distribution has constant hazard:

$$f(t) = \lambda e^{-\lambda t}$$
 
$$S(t) = e^{-\lambda t}$$
 
$$h(t) = \lambda$$

Let's make two generalizations. First, we let the hazard depend on some covariates  $x_1, x_2, \ldots, x_p$ ; we will indicate this dependence by extending our notation for hazard:

$$h(t|x) \stackrel{\text{def}}{=} p(T = t|T \ge t, X = x)$$

Second, we let the base hazard depend on t, but not on the covariates (for now). We can do this using either parametric or semi-parametric approaches.

## 6.1.2. Cox's Proportional Hazards Model

The generalization is that the hazard function is

$$\begin{split} h(t|x) &= h_0(t)\theta(x) \\ \theta(x) &= \exp\left\{\eta(x)\right\} \\ \eta(x) &= x'\beta \\ &\stackrel{\text{def}}{=} \beta_1 x_1 + \dots + \beta_p x_p \end{split}$$

The relationship between h(t|x) and  $\eta(x)$  has a log link (that is,  $\log \{h(t|x)\} = \log \{h_0(t)\} + \eta(x)$ ), as in a generalized linear model.

This model is **semi-parametric**, because the linear predictor depends on estimated parameters but the base hazard function is unspecified. There is no constant term in  $\eta(x)$ , because it is absorbed in the base hazard.

Alternatively, we could define  $\beta_0(t) = \log\{h_0(t)\}$ , and then  $\eta(x,t) = \beta_0(t) + \beta_1 x_1 + \dots + \beta_p x_p$ .

For two different individuals with covariate patterns  $x_1$  and  $x_2$ , the ratio of the hazard functions (a.k.a. **hazard ratio**, a.k.a. **relative hazard**) is:

$$\begin{split} \frac{h(t|x_1)}{h(t|x_2)} &= \frac{h_0(t)\theta(x_1)}{h_0(t)\theta(x_2)} \\ &= \frac{\theta(x_1)}{\theta(x_2)} \end{split}$$

Under the proportional hazards model, this ratio (a.k.a. proportion) does not depend on t. This property is a structural limitation of the model; it is called the **proportional hazards assumption**.

**Definition 6.1** (proportional hazards). A conditional probability distribution p(T|X) has **proportional hazards** if the hazard ratio  $h(t|x_1)/h(t|x_2)$  does not depend on t. Mathematically, it can be written as:

$$\frac{h(t|x_1)}{h(t|x_2)} = \theta(x_1,x_2)$$

As we saw above, Cox's proportional hazards model has this property, with  $\theta(x_1,x_2)=\frac{\theta(x_1)}{\theta(x_2)}$ .

## Note

We are using two similar notations,  $\theta(x_1,x_2)$  and  $\theta(x)$ . We can link these notations if we define  $\theta(x) \stackrel{\text{def}}{=} \theta(x,0)$  and  $\theta(0) = 1$ .

It also has additional notable properties:

$$\begin{split} \frac{h(t|x_1)}{h(t|x_2)} &= \frac{\theta(x_1)}{\theta(x_2)} \\ &= \frac{\exp{\{\eta(x_1)\}}}{\exp{\{\eta(x_2)\}}} \\ &= \exp{\{\eta(x_1) - \eta(x_2)\}} \\ &= \exp{\{x_1'\beta - x_2'\beta\}} \\ &= \exp{\{(x_1 - x_2)'\beta\}} \end{split}$$

Hence on the log scale, we have:

$$\begin{split} \log\left\{\frac{h(t|x_1)}{h(t|x_2)}\right\} &= \eta(x_1) - \eta(x_2) \\ &= x_1'\beta - x_2'\beta \\ &= (x_1 - x_2)'\beta \end{split}$$

If only one covariate  $\boldsymbol{x}_j$  is changing, then:

$$\begin{split} \log \left\{ \frac{h(t|x_1)}{h(t|x_2)} \right\} &= (x_{1j} - x_{2j}) \cdot \beta_j \\ &\propto (x_{1j} - x_{2j}) \end{split}$$

That is, under Cox's model  $h(t|x) = h_0(t) \exp\{x'\beta\}$ , the log of the hazard ratio is proportional to the difference in  $x_j$ , with the proportionality coefficient equal to  $\beta_j$ .

Further,

$$\log \{h(t|x)\} = \log \{h_0(t)\} + x'\beta$$

That is, the covariate effects are additive on the log-hazard scale.

See also:

 $https://en.wikipedia.org/wiki/Proportional\_hazards\_model\#Why\_it\_is\_called\_\%22proportional\%22$ 

#### 6.1.3. Additional properties of the proportional hazards model

If  $h(t|x) = h_0(t)\theta(x)$ , then:

## **6.1.3.1.** Cumulative hazards are also proportional to $H_0(t)$

$$\begin{split} H(t|x) &\stackrel{\text{def}}{=} \int_{u=0}^{t} h(u) du \\ &= \int_{u=0}^{t} h_0(u) \theta(x) du \\ &= \theta(x) \int_{u=0}^{t} h_0(u) du \\ &= \theta(x) H_0(t) \end{split}$$

where  $H_0(t) \stackrel{\text{def}}{=} H(t|0) = \int_{u=0}^t h_0(u) du$ .

## **6.1.3.2.** Survival functions are exponential multiples of $S_0(t)$

$$\begin{split} S(t|x) &= \exp\left\{-H(t|x)\right\} \\ &= \exp\left\{-\theta(x) \cdot H_0(t)\right\} \\ &= \left(\exp\left\{-H_0(t)\right\}\right)^{\theta(x)} \\ &= \left(S_0(t)\right)^{\theta(x)} \end{split}$$

where  $S_0(t) \stackrel{\text{def}}{=} P(T \ge t | X = 0)$  is the survival function for an individual whose covariates are all equal to their default values.

#### 6.1.4. Testing the proportional hazards assumption

The Nelson-Aalen estimate of the cumulative hazard is usually used for estimates of the hazard and often the cumulative hazard.

If the hazards of the three groups are proportional, that means that the ratio of the hazards is constant over t. We can test this using the ratios of the estimated cumulative hazards, which also would be proportional, as shown above.

```
library(KMsurv)
library(survival)
data(bmt)

bmt =
  bmt |>
  as_tibble() |>
  mutate(
   group =
   group |>
  factor(
   labels = c("ALL","Low Risk AML","High Risk AML")))
```

```
nafit = survfit(
  formula = Surv(t2,d3) ~ group,
  type = "fleming-harrington",
  data = bmt)
bmt_curves = tibble(timevec = 1:1000)
sf1 <- with(nafit[1], stepfun(time,c(1,surv)))</pre>
sf2 <- with(nafit[2], stepfun(time,c(1,surv)))</pre>
sf3 <- with(nafit[3], stepfun(time,c(1,surv)))</pre>
bmt_curves =
  bmt_curves |>
  mutate(
    cumhaz1 = -log(sf1(timevec)),
    cumhaz2 = -log(sf2(timevec)),
    cumhaz3 = -log(sf3(timevec)))
library(ggplot2)
bmt_rel_hazard_plot =
  bmt_curves |>
  ggplot(
```

```
Inbrary(ggplot2)
bmt_rel_hazard_plot =
  bmt_curves |>
  ggplot(
    aes(
        x = timevec,
        y = cumhaz1/cumhaz2)
  ) +
  geom_line(aes(col = "ALL/Low Risk AML")) +
  ylab("Hazard Ratio") +
  xlab("Time") +
  ylim(0,6) +
  geom_line(aes(y = cumhaz3/cumhaz1, col = "High Risk AML/ALL")) +
  geom_line(aes(y = cumhaz3/cumhaz2, col = "High Risk AML/Low Risk AML")) +
  theme_bw() +
```

```
labs(colour = "Comparison") +
theme(legend.position="bottom")
print(bmt_rel_hazard_plot)
```

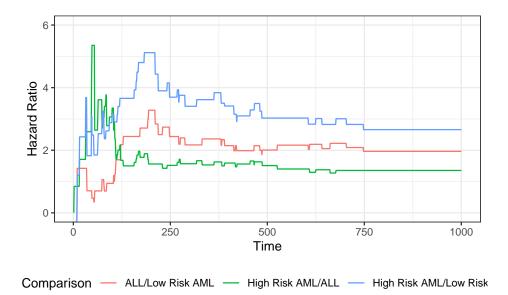


Figure 6.1.: Hazard Ratios by Disease Group

We can zoom in on 30-300 days to take a closer look:

```
bmt_rel_hazard_plot + xlim(c(30,300))
```

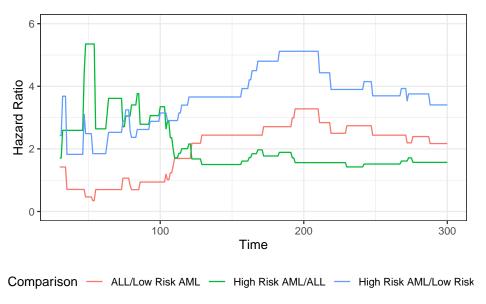


Figure 6.2.: Hazard Ratios by Disease Group (30-300 Days)

#### 6.1.5. Smoothed hazard functions

The Nelson-Aalen estimate of the cumulative hazard is usually used for estimates of the hazard. Since the hazard is the derivative of the cumulative hazard, we need a smooth estimate of the cumulative hazard, which is provided by smoothing the step-function cumulative hazard.

The R package muhaz handles this for us. What we are looking for is whether the hazard function is more or less the same shape, increasing, decreasing, constant, etc. Are the hazards "proportional"?

```
plot(
   survfit(Surv(t2,d3)~group,data=bmt),
   col=1:3,
```

```
lwd=2,
fun="cumhaz",
mark.time = TRUE)
legend("bottomright",c("ALL","Low Risk AML","High Risk AML"),col=1:3,lwd=2)
```



Figure 6.3.: Disease-Free Cumulative Hazard by Disease Group

```
library(muhaz)
muhaz(bmt$t2,bmt$d3,bmt$group=="High Risk AML") |> plot(lwd=2,col=3)
muhaz(bmt$t2,bmt$d3,bmt$group=="ALL") |> lines(lwd=2,col=1)
muhaz(bmt$t2,bmt$d3,bmt$group=="Low Risk AML") |> lines(lwd=2,col=2)
legend("topright",c("ALL","Low Risk AML","High Risk AML"),col=1:3,lwd=2)
```



Figure 6.4.: Smoothed Hazard Rate Estimates by Disease Group

Group 3 was plotted first because it has the highest hazard.

We will see that except for an initial blip in the high risk AML group, the hazards look roughly proportional. They are all strongly decreasing.

#### 6.1.6. Fitting the Proportional Hazards Model

How do we fit a proportional hazards regression model? We need to estimate the coefficients of the covariates, and we need to estimate the base hazard  $h_0(t)$ . For the covariates, supposing for simplicity that there are no tied event times, let the event times for the whole data set be  $t_1, t_2, \ldots, t_D$ . Let the risk set at time  $t_i$  be  $R(t_i)$  and

$$\begin{split} \eta(x) &= \beta_1 x_1 + \dots + \beta_p x_p \\ \theta(x) &= e^{\eta(x)} \\ h(t|X=x) &= h_0(t) e^{\eta(x)} = \theta(x) h_0(t) \end{split}$$

Conditional on a single failure at time t, the probability that the event is due to subject  $f \in R(t)$  is approximately

$$\begin{split} \Pr(f \text{ fails}|1 \text{ failure at } t) &= \frac{h_0(t)e^{\eta(x_f)}}{\sum_{k \in R(t)} h_0(t)e^{\eta(x_f)}} \\ &= \frac{\theta(x_f)}{\sum_{k \in R(t)} \theta(x_k)} \end{split}$$

The logic behind this has several steps. We first fix (ex post) the failure times and note that in this discrete context, the probability  $p_j$  that a subject j in the risk set fails at time t is just the hazard of that subject at that time.

If all of the  $p_i$  are small, the chance that exactly one subject fails is

$$\sum_{k \in R(t)} p_k \left[ \prod_{m \in R(t), m \neq k} (1 - p_m) \right] \approx \sum_{k \in R(t)} p_k$$

If subject i is the one who experiences the event of interest at time  $t_i$ , then the **partial likelihood** is

$$\mathcal{L}^*(\boldsymbol{\beta}|T) = \prod_i \frac{\theta(\boldsymbol{x}_i)}{\sum_{k \in R(t_i)} \theta(\boldsymbol{x}_k)}$$

and we can numerically maximize this with respect to the coefficients  $\beta$  that specify  $\eta(x) = x'\beta$ . When there are tied event times adjustments

need to be made, but the likelihood is still similar. Note that we don't need to know the base hazard to solve for the coefficients.

Once we have coefficient estimates  $\hat{\beta} = (\hat{\beta}_1, \dots, \hat{\beta}_p)$ , this also defines  $\hat{\eta}(x)$  and  $\hat{\theta}(x)$  and then the estimated base cumulative hazard function is

$$\hat{H}(t) = \sum_{t_i < t} \frac{d_i}{\sum_{k \in R(t_i)} \theta(x_k)}$$

which reduces to the Nelson-Aalen estimate when there are no covariates. There are numerous other estimates that have been proposed as well.

## 6.2. Cox Model for the bmt data

#### 6.2.1. Fit the model

```
bmt.cox <- coxph(Surv(t2, d3) ~ group, data = bmt)</pre>
summary(bmt.cox)
Call:
coxph(formula = Surv(t2, d3) ~ group, data = bmt)
 n= 137, number of events= 83
                     coef exp(coef) se(coef)
                                                 z Pr(>|z|)
                                                      0.046 *
groupLow Risk AML
                   -0.574
                              0.563
                                       0.287 - 2.00
groupHigh Risk AML
                              1.467
                                       0.267 1.43
                                                      0.152
                   0.383
Signif. codes: 0 '***' 0.001 '**' 0.05 '.' 0.1 ' ' 1
                   exp(coef) exp(-coef) lower .95 upper .95
```

```
groupLow Risk AML 0.563 1.776 0.321 0.989 groupHigh Risk AML 1.467 0.682 0.869 2.478
```

```
Concordance= 0.625 (se = 0.03)

Likelihood ratio test= 13.4 on 2 df, p=0.001

Wald test = 13 on 2 df, p=0.001

Score (logrank) test = 13.8 on 2 df, p=0.001
```

The table provides hypothesis tests comparing groups 2 and 3 to group 1. Group 3 has the highest hazard, so the most significant comparison is not directly shown.

The coefficient 0.3834 is on the log-hazard-ratio scale, as in log-risk-ratio. The next column gives the hazard ratio 1.4673, and a hypothesis (Wald) test.

The (not shown) group 3 vs. group 2 log hazard ratio is 0.3834 + 0.5742 = 0.9576. The hazard ratio is then  $\exp(0.9576)$  or 2.605.

Inference on all coefficients and combinations can be constructed using coef(bmt.cox) and vcov(bmt.cox) as with logistic and poisson regression.

Concordance is agreement of first failure between pairs of subjects and higher predicted risk between those subjects, omitting non-informative pairs.

The Rsquare value is Cox and Snell's pseudo R-squared and is not very useful.

summary() prints three tests for whether the model with the group covariate is better than the one without

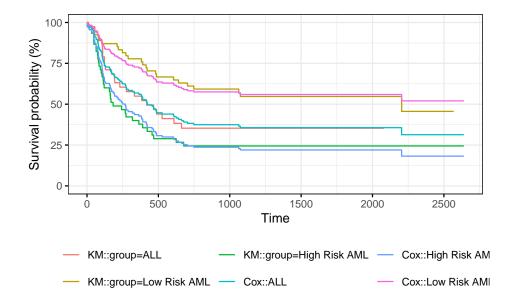
- Likelihood ratio test (chi-squared)
- Wald test (also chi-squared), obtained by adding the squares of the z-scores
- Score = log-rank test, as with comparison of survival functions.

The likelihood ratio test is probably best in smaller samples, followed by the Wald test.

#### 6.2.2. Survival Curves from the Cox Model

We can take a look at the resulting group-specific curves:

```
#| fig-cap: "Survival Functions for Three Groups by KM and Cox Model"
km_fit = survfit(Surv(t2, d3) ~ group, data = as.data.frame(bmt))
cox_fit = survfit(
  bmt.cox,
  newdata =
    data.frame(
      group = unique(bmt$group),
      row.names = unique(bmt$group)))
library(survminer)
list(KM = km_fit, Cox = cox_fit) |>
  survminer::ggsurvplot(
    # facet.by = "group",
    legend = "bottom",
    legend.title = "",
    combine = TRUE,
    fun = 'pct',
    size = .5,
    ggtheme = theme_bw(),
    conf.int = FALSE,
    censor = FALSE) |>
  suppressWarnings() # ggsurvplot() throws some warnings that aren't too worrying
```



When we use survfit() with a Cox model, we have to specify the covariate levels we are interested in; the argument newdata should include a data.frame with the same named columns as the predictors in the Cox model and one or more levels of each.

Otherwise (that is, if the newdata argument is missing), a curve is produced for a single "pseudo" subject with covariate values equal to the means component of the fit.

The resulting curve(s) almost never make sense, but the default remains due to an unwarranted attachment to the option shown by some users and by other packages.

Two particularly egregious examples are factor variables and interactions. Suppose one were studying interspecies transmission of a virus, and the data set has a factor variable with levels ("pig", "chicken") and about equal numbers of observations for each. The "mean" covariate level will be 0.5 – is this a flying pig?

## 6.2.3. Examining survfit

230

23

1

```
survfit(Surv(t2, d3)~group,data=bmt)
Call: survfit(formula = Surv(t2, d3) ~ group, data = bmt)
                      n events median 0.95LCL 0.95UCL
group=ALL
                            24
                                   418
                                           194
                     38
                                                     NA
                                           704
group=Low Risk AML
                     54
                            25
                                  2204
                                                     NA
group=High Risk AML 45
                            34
                                   183
                                           115
                                                    456
survfit(Surv(t2, d3)~group, data=bmt) |> summary()
Call: survfit(formula = Surv(t2, d3) ~ group, data = bmt)
                group=ALL
time n.risk n.event survival std.err lower 95% CI upper 95% CI
    1
          38
                    1
                         0.974
                                0.0260
                                               0.924
                                                             1.000
   55
          37
                    1
                         0.947
                                                             1.000
                                0.0362
                                               0.879
   74
                    1
                         0.921
                                                             1.000
          36
                                0.0437
                                               0.839
   86
          35
                    1
                         0.895
                                0.0498
                                               0.802
                                                             0.998
                                0.0548
  104
                         0.868
          34
                                               0.767
                                                             0.983
  107
          33
                    1
                         0.842
                                0.0592
                                               0.734
                                                             0.966
                                                             0.949
  109
                    1
                         0.816
                                0.0629
          32
                                               0.701
  110
          31
                    1
                         0.789
                                0.0661
                                               0.670
                                                             0.930
  122
          30
                    2
                         0.737
                                               0.609
                                                             0.891
                                0.0714
  129
          28
                    1
                         0.711
                                0.0736
                                               0.580
                                                             0.870
  172
          27
                    1
                         0.684 0.0754
                                               0.551
                                                             0.849
  192
                    1
                         0.658 0.0770
                                                             0.827
          26
                                               0.523
                    1
                         0.632 0.0783
  194
          25
                                               0.495
                                                             0.805
```

0.604 0.0795

0.467

0.782

276	22	1	0.577	0.0805	0.439	0.758
332	21	1	0.549	0.0812	0.411	0.734
383	20	1	0.522	0.0817	0.384	0.709
418	19	1	0.494	0.0819	0.357	0.684
466	18	1	0.467	0.0818	0.331	0.658
487	17	1	0.439	0.0815	0.305	0.632
526	16	1	0.412	0.0809	0.280	0.605
609	14	1	0.382	0.0803	0.254	0.577
662	13	1	0.353	0.0793	0.227	0.548
		group	p=Low Risl	k AML		
time	n.risk	n.event	survival	std.err	lower 95% CI	upper 95% CI

		0 1	•						
time	${\tt n.risk}$	${\tt n.event}$	survival	std.err	lower	95% CI	upper	95%	CI
10	54	1	0.981	0.0183		0.946		1.	000
35	53	1	0.963	0.0257		0.914		1.	000
48	52	1	0.944	0.0312		0.885		1.	000
53	51	1	0.926	0.0356		0.859		0.9	998
79	50	1	0.907	0.0394		0.833		0.9	988
80	49	1	0.889	0.0428		0.809		0.9	977
105	48	1	0.870	0.0457		0.785		0.9	965
211	47	1	0.852	0.0483		0.762		0.9	952
219	46	1	0.833	0.0507		0.740		0.9	939
248	45	1	0.815	0.0529		0.718		0.9	925
272	44	1	0.796	0.0548		0.696		0.9	911
288	43	1	0.778	0.0566		0.674		0.8	397
381	42	1	0.759	0.0582		0.653		0.8	882
390	41	1	0.741	0.0596		0.633		0.8	367
414	40	1	0.722	0.0610		0.612		0.8	352
421	39	1	0.704	0.0621		0.592		0.8	337
481	38	1	0.685	0.0632		0.572		0.8	321
486	37	1	0.667	0.0642		0.552		0.8	305
606	36	1	0.648	0.0650		0.533		0.	789
641	35	1	0.630	0.0657		0.513		0.	773
704	34	1	0.611	0.0663		0.494		0.	756
748	33	1	0.593	0.0669		0.475		0.	739

1063	26	1	0.570	0.0681	0.451	0.720			
1074	25	1	0.547	0.0691	0.427	0.701			
2204	6	1	0.456	0.1012	0.295	0.704			
group=High Risk AML									
time	${\tt n.risk}$	${\tt n.event}$	survival	${\tt std.err}$	lower 95% CI	upper 95% CI			
2	45	1	0.978	0.0220	0.936	1.000			
16	44	1	0.956	0.0307	0.897	1.000			
32	43	1	0.933	0.0372	0.863	1.000			
47	42	2	0.889	0.0468	0.802	0.986			
48	40	1	0.867	0.0507	0.773	0.972			
63	39	1	0.844	0.0540	0.745	0.957			
64	38	1	0.822	0.0570	0.718	0.942			
74	37	1	0.800	0.0596	0.691	0.926			
76	36	1	0.778	0.0620	0.665	0.909			
80	35	1	0.756	0.0641	0.640	0.892			
84	34	1	0.733	0.0659	0.615	0.875			
93	33	1	0.711	0.0676	0.590	0.857			
100	32	1	0.689	0.0690	0.566	0.838			
105	31	1	0.667	0.0703	0.542	0.820			
113	30	1	0.644	0.0714	0.519	0.801			
115	29	1	0.622	0.0723	0.496	0.781			
120	28	1	0.600	0.0730	0.473	0.762			
157	27	1	0.578	0.0736	0.450	0.742			
162	26	1	0.556	0.0741	0.428	0.721			
164	25	1	0.533	0.0744	0.406	0.701			
168	24	1	0.511	0.0745	0.384	0.680			
183	23	1	0.489	0.0745	0.363	0.659			
242	22	1	0.467	0.0744	0.341	0.638			
268	21	1	0.444	0.0741	0.321	0.616			
273	20	1	0.422	0.0736	0.300	0.594			
318	19	1	0.400	0.0730	0.280	0.572			
363	18	1	0.378	0.0723	0.260	0.550			

0.356 0.0714

0.240

0.527

1

390

17

```
422
        16
                      0.333 0.0703
                                            0.221
                                                         0.504
                 1
456
        15
                 1
                      0.311 0.0690
                                            0.201
                                                         0.481
467
                      0.289 0.0676
                                            0.183
                                                         0.457
        14
625
        13
                 1
                     0.267 0.0659
                                            0.164
                                                         0.433
677
        12
                 1
                      0.244 0.0641
                                            0.146
                                                         0.409
```

```
survfit(bmt.cox)
Call: survfit(formula = bmt.cox)
       n events median 0.95LCL 0.95UCL
[1,] 137
             83
                   422
                           268
                                    NA
survfit(bmt.cox, newdata = tibble(group = unique(bmt$group)))
Call: survfit(formula = bmt.cox, newdata = tibble(group = unique(bmt$group)))
    n events median 0.95LCL 0.95UCL
1 137
          83
                422
                        268
2 137
          83
                 NA
                        625
                                 NA
3 137
          83
                268
                        162
                                467
bmt.cox |>
  survfit(newdata = tibble(group = unique(bmt$group))) |>
  summary()
Call: survfit(formula = bmt.cox, newdata = tibble(group = unique(bmt$group)))
 time n.risk n.event survival1 survival2 survival3
    1
         137
                         0.993
                                   0.996
                                              0.989
                   1
    2
         136
                   1
                         0.985
                                   0.992
                                              0.978
```

10	135	1	0.978	0.987	0.968
16	134	1	0.970	0.983	0.957
32	133	1	0.963	0.979	0.946
35	132	1	0.955	0.975	0.935
47	131	2	0.941	0.966	0.914
48	129	2	0.926	0.957	0.893
53	127	1	0.918	0.953	0.882
55	126	1	0.911	0.949	0.872
63	125	1	0.903	0.944	0.861
64	124	1	0.896	0.940	0.851
74	123	2	0.881	0.931	0.830
76	121	1	0.873	0.926	0.819
79	120	1	0.865	0.922	0.809
80	119	2	0.850	0.913	0.788
84	117	1	0.843	0.908	0.778
86	116	1	0.835	0.903	0.768
93	115	1	0.827	0.899	0.757
100	114	1	0.820	0.894	0.747
104	113	1	0.812	0.889	0.737
105	112	2	0.797	0.880	0.717
107	110	1	0.789	0.875	0.707
109	109	1	0.782	0.870	0.697
110	108	1	0.774	0.866	0.687
113	107	1	0.766	0.861	0.677
115	106	1	0.759	0.856	0.667
120	105	1	0.751	0.851	0.657
122	104	2	0.735	0.841	0.637
129	102	1	0.727	0.836	0.627
157	101	1	0.720	0.831	0.617
162	100	1	0.712	0.826	0.607
164	99	1	0.704	0.821	0.598
168	98	1	0.696	0.815	0.588
172	97	1	0.688	0.810	0.578
183	96	1	0.680	0.805	0.568

192	95	1	0.672	0.800	0.558
194	94	1	0.664	0.794	0.549
211	93	1	0.656	0.789	0.539
219	92	1	0.648	0.783	0.530
230	90	1	0.640	0.778	0.520
242	89	1	0.632	0.773	0.511
248	88	1	0.624	0.767	0.501
268	87	1	0.616	0.761	0.492
272	86	1	0.608	0.756	0.482
273	85	1	0.600	0.750	0.473
276	84	1	0.592	0.745	0.464
288	83	1	0.584	0.739	0.454
318	82	1	0.576	0.733	0.445
332	81	1	0.568	0.727	0.436
363	80	1	0.560	0.722	0.427
381	79	1	0.552	0.716	0.418
383	78	1	0.544	0.710	0.409
390	77	2	0.528	0.698	0.392
414	75	1	0.520	0.692	0.383
418	74	1	0.512	0.686	0.374
421	73	1	0.504	0.680	0.366
422	72	1	0.496	0.674	0.357
456	71	1	0.488	0.667	0.349
466	70	1	0.480	0.661	0.340
467	69	1	0.472	0.655	0.332
481	68	1	0.464	0.649	0.324
486	67	1	0.455	0.642	0.315
487	66	1	0.447	0.636	0.307
526	65	1	0.439	0.629	0.299
606	63	1	0.431	0.623	0.291
609	62	1	0.423	0.616	0.283
625	61	1	0.415	0.609	0.275
641	60	1	0.407	0.603	0.267
662	59	1	0.399	0.596	0.260

#### 6. Proportional Hazards Models

677	58	1	0.391	0.589	0.252
704	57	1	0.383	0.582	0.244
748	56	1	0.374	0.575	0.237
1063	47	1	0.365	0.567	0.228
1074	46	1	0.356	0.559	0.220
2204	9	1	0.313	0.520	0.182

### 6.3. Adjustment for Ties (optional)

#### 6.3.1.

At each time  $t_i$  at which more than one of the subjects has an event, let  $d_i$  be the number of events at that time,  $D_i$  the set of subjects with events at that time, and let  $s_i$  be a covariate vector for an artificial subject obtained by adding up the covariate values for the subjects with an event at time  $t_i$ . Let

$$\bar{\eta}_i = \beta_1 s_{i1} + \dots + \beta_p s_{ip}$$

and 
$$\bar{\theta}_i = \exp{\{\bar{\eta}_i\}}$$
.

Let  $s_i$  be a covariate vector for an artificial subject obtained by adding up the covariate values for the subjects with an event at time  $t_i$ . Note that

$$\begin{split} \bar{\eta}_i &= \sum_{j \in D_i} \beta_1 x_{j1} + \dots + \beta_p x_{jp} \\ &= \beta_1 s_{i1} + \dots + \beta_p s_{ip} \\ \bar{\theta}_i &= \exp\left\{\bar{\eta}_i\right\} \\ &= \prod_{j \in D_i} \theta_i \end{split}$$

#### 6.3.1.1. Breslow's method for ties

Breslow's method estimates the partial likelihood as

$$\begin{split} L(\beta|T) &= \prod_i \frac{\bar{\theta}_i}{[\sum_{k \in R(t_i)} \theta_k]^{d_i}} \\ &= \prod_i \prod_{j \in D_i} \frac{\theta_j}{\sum_{k \in R(t_i)} \theta_k} \end{split}$$

This method is equivalent to treating each event as distinct and using the non-ties formula. It works best when the number of ties is small. It is the default in many statistical packages, including PROC PHREG in SAS.

#### 6.3.1.2. Efron's method for ties

The other common method is Efron's, which is the default in R.

$$L(\beta|T) = \prod_i \frac{\bar{\theta}_i}{\prod_{j=1}^{d_i} [\sum_{k \in R(t_i)} \theta_k - \frac{j-1}{d_i} \sum_{k \in D_i} \theta_k]}$$

This is closer to the exact discrete partial likelihood when there are many ties.

The third option in R (and an option also in SAS as discrete) is the "exact" method, which is the same one used for matched logistic regression.

#### 6.3.1.3. Example: Breslow's method

Suppose as an example we have a time t where there are 20 individuals at risk and three failures. Let the three individuals have risk parameters

#### 6. Proportional Hazards Models

 $\theta_1, \theta_2, \theta_3$  and let the sum of the risk parameters of the remaining 17 individuals be  $\theta_R$ . Then the factor in the partial likelihood at time t using Breslow's method is

$$\left(\frac{\theta_1}{\theta_R+\theta_1+\theta_2+\theta_3}\right)\left(\frac{\theta_2}{\theta_R+\theta_1+\theta_2+\theta_3}\right)\left(\frac{\theta_3}{\theta_R+\theta_1+\theta_2+\theta_3}\right)$$

If on the other hand, they had died in the order 1,2, 3, then the contribution to the partial likelihood would be:

$$\left(\frac{\theta_1}{\theta_R + \theta_1 + \theta_2 + \theta_3}\right) \left(\frac{\theta_2}{\theta_R + \theta_2 + \theta_3}\right) \left(\frac{\theta_3}{\theta_R + \theta_3}\right)$$

as the risk set got smaller with each failure. The exact method roughly averages the results for the six possible orderings of the failures.

#### 6.3.1.4. Example: Efron's method

But we don't know the order they failed in, so instead of reducing the denominator by one risk coefficient each time, we reduce it by the same fraction. This is Efron's method.

$$\left(\frac{\theta_1}{\theta_R+\theta_1+\theta_2+\theta_3}\right)\left(\frac{\theta_2}{\theta_R+2(\theta_1+\theta_2+\theta_3)/3}\right)\left(\frac{\theta_3}{\theta_R+(\theta_1+\theta_2+\theta_3)/3}\right)$$

#### Configuring R

Functions from these packages will be used throughout this document:

```
library(pander) # format tables for markdown
library(ggplot2) # graphics
library(ggfortify) # help with graphics
library(ggeasy) # help with graphics
library(survival) # survival analysis
library(survminer) # survival analysis graphics
library(dplyr) # manipulate data
library(haven) # import Stata files
library(knitr) # format R output for markdown
library(tidyr) # Tools to help to create tidy data
library(plotly) # interactive graphics
library(dobson) # datasets from Dobson and Barnett 2018
library(fs) # filesystem path manipulations
library(KMsurv) # datasets from Klein and Moeschberger
library(parameters) # format model output tables for markdown
library(conflicted) # check for conflicting function definitions
conflicts_prefer(dplyr::filter)
conflicts_prefer(ggplot2::autoplot)
```

Here are some R settings I use in this document:

```
rm(list = ls()) # delete any data that's already loaded into R
knitr::opts_chunk$set(message = FALSE)
pander::panderOptions("table.emphasize.rownames", FALSE)
options('digits' = 4)
legend_text_size = 9
```

#### 7.1. Building Cox Proportional Hazards models

#### 7.1.1. hodg Lymphoma Data Set from KMsurv

#### 7.1.1.1. Participants

43 bone marrow transplant patients at Ohio State University (Avalos 1993)

#### **7.1.1.2.** Variables

- dtype: Disease type (Hodgkin's or non-Hodgkins lymphoma)
- gtype: Bone marrow graft type:
- allogeneic: from HLA-matched sibling
- autologous: from self (prior to chemo)
- time: time to study exit
- delta: study exit reason (death/relapse vs censored)
- wtime: waiting time to transplant (in months)
- score: Karnofsky score:
- 80–100: Able to carry on normal activity and to work; no special care needed.
- 50–70: Unable to work; able to live at home and care for most personal needs; varying amount of assistance needed.
- 10–60: Unable to care for self; requires equivalent of institutional or hospital care; disease may be progressing rapidly.

#### 7.1.1.3. Data

```
data(hodg, package = "KMsurv")
hodg2 = hodg >
  as_tibble() |>
  mutate(
    # We add factor labels to the categorical variables:
    gtype = gtype |>
      case_match(
        1 ~ "Allogenic",
        2 ~ "Autologous"),
    dtype = dtype |>
      case_match(
        1 ~ "Non-Hodgkins",
        2 ~ "Hodgkins") |>
      factor() |>
      relevel(ref = "Non-Hodgkins"),
    delta = delta |>
      case_match(
        1 ~ "dead",
        0 ~ "alive"),
    surv = Surv(
      time = time,
      event = delta == "dead")
hodg2 |> print()
```

```
# A tibble: 43 x 7
             dtype
                           time delta score wtime
  gtype
   <chr>
             <fct>
                          <int> <chr> <int> <int> <Surv>
1 Allogenic Non-Hodgkins
                             28 dead
                                                24
                                          90
                                                      28
                                                 7
2 Allogenic Non-Hodgkins
                             32 dead
                                          30
                                                      32
```

```
8
                                                     49
3 Allogenic Non-Hodgkins
                             49 dead
                                         40
                                                     84
4 Allogenic Non-Hodgkins
                             84 dead
                                         60
                                               10
                                         70
5 Allogenic Non-Hodgkins
                            357 dead
                                               42
                                                    357
6 Allogenic Non-Hodgkins
                            933 alive
                                         90
                                               9
                                                    933+
7 Allogenic Non-Hodgkins 1078 alive
                                        100
                                               16
                                                   1078+
8 Allogenic Non-Hodgkins 1183 alive
                                         90
                                               16
                                                   1183+
9 Allogenic Non-Hodgkins
                          1560 alive
                                         80
                                               20
                                                   1560+
10 Allogenic Non-Hodgkins
                                               27
                          2114 alive
                                         80
                                                   2114+
# i 33 more rows
```

#### 7.1.2. Proportional hazards model

```
hodg.cox1 = coxph(
  formula = surv ~ gtype * dtype + score + wtime,
  data = hodg2)
summary(hodg.cox1)
```

```
Call:
coxph(formula = surv ~ gtype * dtype + score + wtime, data = hodg2)
 n= 43, number of events= 26
```

```
coef exp(coef) se(coef)
                                                             z Pr(>|z|)
gtypeAutologous
                               0.6394
                                        1.8953
                                                  0.5937 1.08
                                                                 0.2815
                                                  0.9474 2.91
dtypeHodgkins
                               2.7603
                                        15.8050
                                                                 0.0036 **
                              -0.0495
                                        0.9517
                                                  0.0124 -3.98 6.8e-05 ***
score
wtime
                              -0.0166
                                         0.9836
                                                  0.0102 - 1.62
                                                                 0.1046
gtypeAutologous:dtypeHodgkins -2.3709
                                         0.0934
                                                  1.0355 -2.29
                                                                 0.0220 *
Signif. codes: 0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
```

```
exp(coef) exp(-coef) lower .95 upper .95
gtypeAutologous
                               1.8953
                                         0.5276
                                                   0.5920
                                                              6.068
dtypeHodgkins
                              15.8050
                                         0.0633
                                                   2.4682
                                                            101.207
score
                               0.9517
                                        1.0507
                                                   0.9288
                                                             0.975
                               0.9836
                                         1.0167
                                                   0.9641
                                                             1.003
wtime
gtypeAutologous:dtypeHodgkins
                               0.0934
                                         10.7074
                                                   0.0123
                                                             0.711
Concordance= 0.776 (se = 0.059)
Likelihood ratio test= 32.1 on 5 df,
                                     p=6e-06
Wald test
                   = 27.2 on 5 df,
                                      p=5e-05
Score (logrank) test = 37.7 on 5 df,
                                      p=4e-07
```

## 7.2. Diagnostic graphs for proportional hazards assumption

#### 7.2.1. Analysis plan

- survival function for the four combinations of disease type and graft type.
- observed (nonparametric) vs. expected (semiparametric) survival functions.
- complementary log-log survival for the four groups.

#### 7.2.2. Kaplan-Meier survival functions

```
km_model = survfit(
  formula = surv ~ dtype + gtype,
  data = hodg2)
```

```
km_model |>
  autoplot(conf.int = FALSE) +
  theme_bw() +
  theme(
    legend.position="bottom",
    legend.title = element_blank(),
    legend.text = element_text(size = legend_text_size)
) +
  guides(col=guide_legend(ncol=2)) +
  ylab('Survival probability, S(t)') +
  xlab("Time since transplant (days)")
```

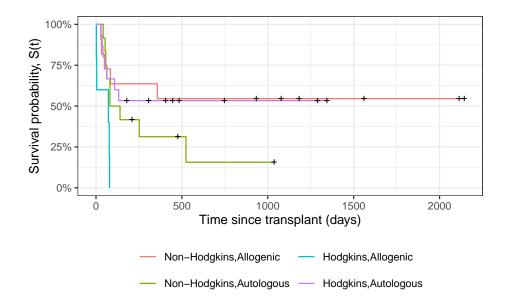


Figure 7.1.: Kaplan-Meier Survival Curves for HOD/NHL and Allo/Auto Grafts

#### 7.2.3. Observed and expected survival curves

```
# we need to create a tibble of covariate patterns;
# we will set score and wtime to mean values for disease and graft types:
means = hodg2 |>
  summarize(
    .by = c(dtype, gtype),
    score = mean(score),
   wtime = mean(wtime)) |>
  arrange(dtype, gtype) |>
  mutate(strata = paste(dtype, gtype, sep = ",")) |>
  as.data.frame()
# survfit.coxph() will use the rownames of its `newdata`
# argument to label its output:
rownames(means) = means$strata
cox_model =
 hodg.cox1 |>
  survfit(
    data = hodg2, # ggsurvplot() will need this
    newdata = means)
# I couldn't find a good function to reformat `cox_model` for ggplot,
# so I made my own:
stack_surv_ph = function(cox_model)
  cox_model$surv |>
    as_tibble() |>
    mutate(time = cox_model$time) |>
   pivot_longer(
      cols = -time,
      names_to = "strata",
```

```
values_to = "surv") |>
mutate(
    cumhaz = -log(surv),
    model = "Cox PH")
}

km_and_cph =
    km_model |>
    fortify(surv.connect = TRUE) |>
    mutate(
        strata = trimws(strata),
        model = "Kaplan-Meier",
        cumhaz = -log(surv)) |>
    bind_rows(stack_surv_ph(cox_model))
```

```
km_and_cph |>
  ggplot(aes(x = time, y = surv, col = model)) +
  geom_step() +
  facet_wrap(~strata) +
  theme_bw() +
  ylab("S(t) = P(T>=t)") +
  xlab("Survival time (t, days)") +
  theme(legend.position = "bottom")
```



Figure 7.2.: Observed and expected survival curves for bmt data

#### 7.2.4. Cumulative hazard (log-scale) curves

Also known as "complementary log-log (clog-log) survival curves".

```
na_model = survfit(
  formula = surv ~ dtype + gtype,
  data = hodg2,
  type = "fleming")

na_model |>
  survminer::ggsurvplot(
  legend = "bottom",
  legend.title = "",
```

```
ylab = "log(Cumulative Hazard)",
xlab = "Time since transplant (days, log-scale)",
fun = 'cloglog',
size = .5,
ggtheme = theme_bw(),
conf.int = FALSE,
censor = TRUE) |>
magrittr::extract2("plot") +
guides(
    col =
        guide_legend(
        ncol = 2,
        label.theme =
        element_text(
        size = legend_text_size)))
```



Figure 7.3.: Complementary log-log survival curves - Nelson-Aalen estimates

Let's compare these empirical (i.e., non-parametric) curves with the fitted curves from our coxph() model:

```
cox_model |>
survminer::ggsurvplot(
  facet_by = "",
  legend = "bottom",
  legend.title = "",
  ylab = "log(Cumulative Hazard)",
  xlab = "Time since transplant (days, log-scale)",
  fun = 'cloglog',
  size = .5,
  ggtheme = theme_bw(),
```

```
censor = FALSE, # doesn't make sense for cox model
  conf.int = FALSE) |>
magrittr::extract2("plot") +
guides(
  col =
    guide_legend(
    ncol = 2,
    label.theme =
    element_text(
        size = legend_text_size)))
```



Figure 7.4.: Complementary log-log survival curves - PH estimates

Now let's overlay these cumulative hazard curves:

```
na_and_cph =
 na_model |>
  fortify(fun = "cumhaz") |>
 # `fortify.survfit()` doesn't name cumhaz correctly:
 rename(cumhaz = surv) |>
  mutate(
    surv = exp(-cumhaz),
    strata = trimws(strata)) |>
  mutate(model = "Nelson-Aalen") |>
  bind_rows(stack_surv_ph(cox_model))
na_and_cph |>
  ggplot(
    aes(
     x = time,
     y = cumhaz,
      col = model)) +
  geom_step() +
  facet_wrap(~strata) +
  theme_bw() +
  scale_y_continuous(
   trans = "log10",
   name = "Cumulative hazard H(t) (log-scale)") +
  scale_x_continuous(
   trans = "log10",
   name = "Survival time (t, days, log-scale)") +
  theme(legend.position = "bottom")
```

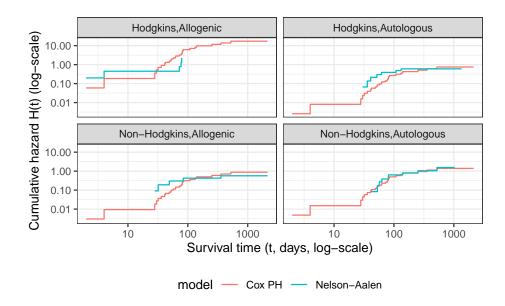


Figure 7.5.: Observed and expected cumulative hazard curves for bmt data (cloglog format)

#### 7.3. Predictions and Residuals

#### 7.3.1. Review: Predictions in Linear Regression

• In linear regression, we have a linear predictor for each data point i

$$\begin{split} &\eta_i = \beta_0 + \beta_1 x_{1i} + \dots + \beta_p x_{pi} \\ &\hat{y}_i = \hat{\eta}_i = \hat{\beta}_0 + \hat{\beta}_1 x_{1i} + \dots + \hat{\beta}_p x_{pi} \\ &y_i \sim N(\eta_i, \sigma^2) \end{split}$$

•  $\hat{y}_i$  estimates the conditional mean of  $y_i$  given the covariate values  $\tilde{x}_i$ . This together with the prediction error says that we are predicting the distribution of values of y.

#### 7.3.2. Review: Residuals in Linear Regression

- The usual residual is  $r_i = y_i \hat{y}_i$ , the difference between the actual value of y and a prediction of its mean.
- The residuals are also the quantities the sum of whose squares is being minimized by the least squares/MLE estimation.

#### 7.3.3. Predictions and Residuals in survival models

- In survival analysis, the equivalent of  $y_i$  is the event time  $t_i$ , which is unknown for the censored observations.
- The expected event time can be tricky to calculate:

$$\hat{\mathbf{E}}[T|X=x] = \int_{t=0}^{\infty} \hat{S}(t)dt$$

#### 7.3.4. Wide prediction intervals

The nature of time-to-event data results in very wide prediction intervals:

- Suppose a cancer patient is predicted to have a mean lifetime of 5 years after diagnosis and suppose the distribution is exponential.
- If we want a 95% interval for survival, the lower end is at the 0.025 percentage point of the exponential which is qexp(.025, rate = 1/5) = 0.12658904 years, or 1/40 of the mean lifetime.

- The upper end is at the 0.975 point which is qexp(.975, rate = 1/5) = 18.44439727 years, or 3.7 times the mean lifetime.
- Saying that the survival time is somewhere between 6 weeks and 18 years does not seem very useful, but it may be the best we can do.
- For survival analysis, something is like a residual if it is small when the model is accurate or if the accumulation of them is in some way minimized by the estimation algorithm, but there is no exact equivalence to linear regression residuals.
- And if there is, they are mostly quite large!

#### 7.3.5. Types of Residuals in Time-to-Event Models

- It is often hard to make a decision from graph appearances, though the process can reveal much.
- Some diagnostic tests are based on residuals as with other regression methods:
- Schoenfeld residuals (via cox.zph) for proportionality.
- Cox-Snell residuals for goodness of fit.
- martingale residuals for non-linearity.
- dfbeta for influence.

#### 7.3.6. Schoenfeld residuals

- There is a Schoenfeld residual for each subject i with an event (not censored) and for each predictor  $x_k$ .
- At the event time t for that subject, there is a risk set R, and each subject j in the risk set has a risk coefficient  $\theta_j$  and also a value  $x_{jk}$  of the predictor.
- The Schoenfeld residual is the difference between  $x_{ik}$  and the risk-weighted average of all the  $x_{ik}$  over the risk set.

$$r_{ik}^S = x_{ik} - \frac{\sum_{k \in R} x_{jk} \theta_k}{\sum_{k \in R} \theta_k}$$

This residual measures how typical the individual subject is with respect to the covariate at the time of the event. Since subjects should fail more or less uniformly according to risk, the Schoenfeld residuals should be approximately level over time, not increasing or decreasing.

We can test this with the correlation with time on some scale, which could be the time itself, the log time, or the rank in the set of failure times.

The default is to use the KM curve as a transform, which is similar to the rank but deals better with censoring.

The cox.zph() function implements a score test proposed in Grambsch and Therneau (1994).

```
hodg.zph = cox.zph(hodg.cox1)
print(hodg.zph)
```

	chisq	df	р
gtype	0.5400	1	0.462
dtype	1.8012	1	0.180
score	3.8805	1	0.049
wtime	0.0173	1	0.895
<pre>gtype:dtype</pre>	4.0474	1	0.044
GLOBAL	13.7573	5	0.017

#### 7.3.6.1. gtype

```
ggcoxzph(hodg.zph, var = "gtype")
```

Global Schoenfeld Test p: 0.01723

## Schoenfeld Individual Test p: 0.4624

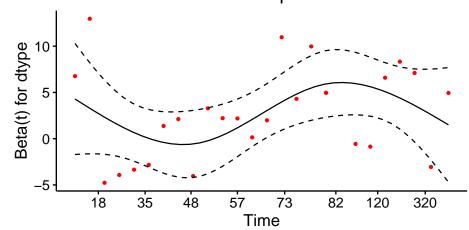


#### **7.3.6.2.** dtype

ggcoxzph(hodg.zph, var = "dtype")

Global Schoenfeld Test p: 0.01723

## Schoenfeld Individual Test p: 0.1796



#### **7.3.6.3.** score

ggcoxzph(hodg.zph, var = "score")

Global Schoenfeld Test p: 0.01723

## Schoenfeld Individual Test p: 0.0489



#### 7.3.6.4. wtime

ggcoxzph(hodg.zph, var = "wtime")

Global Schoenfeld Test p: 0.01723

## Schoenfeld Individual Test p: 0.8954

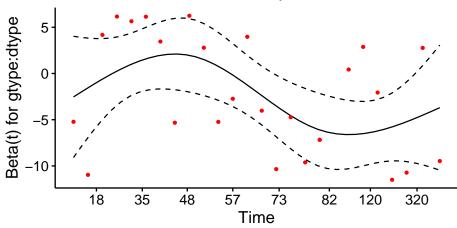


#### **7.3.6.5**. gtype:dtype

ggcoxzph(hodg.zph, var = "gtype:dtype")

Global Schoenfeld Test p: 0.01723





#### 7.3.6.6. Conclusions

- From the correlation test, the Karnofsky score and the interaction with graft type disease type induce modest but statistically significant non-proportionality.
- The sample size here is relatively small (26 events in 43 subjects). If the sample size is large, very small amounts of non-proportionality can induce a significant result.
- As time goes on, autologous grafts are over-represented at their own event times, but those from HOD patients become less represented.
- Both the statistical tests and the plots are useful.

#### 7.4. Goodness of Fit using the Cox-Snell Residuals

(references: Klein & Moeschberger textbook, §11.2, and Dobson & Barnett textbook, §10.6)

Suppose that an individual has a survival time T which has survival function S(t), meaning that  $\Pr(T > t) = S(t)$ . Then S(T) has a uniform distribution on (0,1).

$$\begin{split} \Pr(S(T_i) \leq u) &= \Pr(T_i > S_i^{-1}(u)) \\ &= S_i(S_i^{-1}(u)) \\ &= u \end{split}$$

Also, if U has a uniform distribution on (0,1), then what is the distribution of  $-\ln(U)$ ?

$$\Pr(-\ln(U) < x) = \Pr(U > \exp\{-x\})$$
  
= 1 - e<sup>-x</sup>

which is the CDF of an exponential distribution with parameter  $\lambda=1.$  So,

$$r_i^{CS} \stackrel{\text{def}}{=} -\ln[\hat{S}(t_i|x_i)] = \hat{H}(t_i|\tilde{x}_i)$$

should have an exponential distribution with constant hazard  $\lambda=1$  if the estimate  $\hat{S}_i$  is accurate, which means that these values should look like a censored sample from this exponential distribution. These values are called **generalized residuals** or **Cox-Snell residuals**.

```
hodg2 = hodg2 |>
  mutate(cs = predict(hodg.cox1, type = "expected"))

surv.csr = survfit(
  data = hodg2,
  formula = Surv(time = cs, event = delta == "dead") ~ 1,
  type = "fleming-harrington")

autoplot(surv.csr, fun = "cumhaz") +
  geom_abline(aes(intercept = 0, slope = 1), col = "red") +
  theme_bw()
```



Figure 7.6.: Cumulative Hazard of Cox-Snell Residuals

The line with slope 1 and intercept 0 fits the curve relatively well, so we

don't see lack of fit using this procedure.

#### 7.5. Martingale Residuals

The martingale residuals are a slight modification of the Cox-Snell residuals. If the censoring indicator is  $\delta_i$ , then

$$r_i^M = \delta_i - r_i^{CS}$$

These residuals can be interpreted as an estimate of the excess number of events seen in the data but not predicted by the model. We will use these to examine the functional forms of continuous covariates.

#### 7.5.1. Using Martingale Residuals

Martingale residuals can be used to examine the functional form of a numeric variable.

- We fit the model without that variable and compute the martingale residuals.
- We then plot these martingale residuals against the values of the variable.
- We can see curvature, or a possible suggestion that the variable can be discretized.

Let's use this to examine the score and wtime variables in the wtime data set.

#### Karnofsky score

```
hodg2 = hodg2 |>
mutate(
    mres =
    hodg.cox1 |>
    update(. ~ . - score) |>
    residuals(type="martingale"))

hodg2 |>
    ggplot(aes(x = score, y = mres)) +
    geom_point() +
    geom_smooth(method = "loess", aes(col = "loess")) +
    geom_smooth(method = 'lm', aes(col = "lm")) +
    theme_classic() +
    xlab("Karnofsky Score") +
    ylab("Martingale Residuals") +
    guides(col=guide_legend(title = ""))
```



Figure 7.7.: Martingale Residuals vs. Karnofsky Score

The line is almost straight. It could be some modest transformation of the Karnofsky score would help, but it might not make much difference.

#### Waiting time

```
hodg2$mres =
hodg.cox1 |>
update(. ~ . - wtime) |>
residuals(type="martingale")

hodg2 |>
ggplot(aes(x = wtime, y = mres)) +
```

```
geom_point() +
geom_smooth(method = "loess", aes(col = "loess")) +
geom_smooth(method = 'lm', aes(col = "lm")) +
theme_classic() +
xlab("Waiting Time") +
ylab("Martingale Residuals") +
guides(col=guide_legend(title = ""))
```

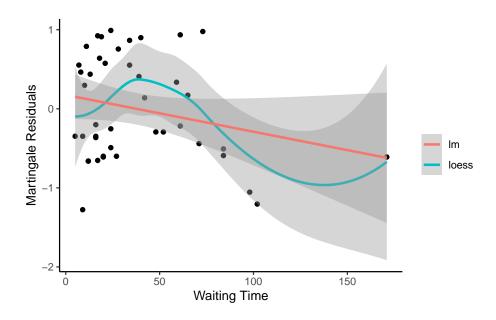


Figure 7.8.: Martingale Residuals vs. Waiting Time

The line could suggest a step function. To see where the drop is, we can look at the largest waiting times and the associated martingale residual.

The martingale residuals are all negative for  $\mathtt{wtime} > 83$  and positive for the next smallest value. A reasonable cut-point is 80 days.

#### Updating the model

Let's reformulate the model with dichotomized wtime.

```
hodg2 =
hodg2 |>
mutate(
    wt2 = cut(
        wtime,c(0, 80, 200),
        labels=c("short","long")))

hodg.cox2 =
    coxph(
    formula =
        Surv(time, event = delta == "dead") ~
        gtype*dtype + score + wt2,
        data = hodg2)
```

```
hodg.cox1 |> drop1(test="Chisq")
```

Table 7.1.: Model summary table with waiting time on continuous scale

	$\operatorname{Df}$	AIC	LRT	$\Pr(>\text{Chi})$
	NA	152.4	NA	NA
score	1	167.6	17.236	0.0000
wtime	1	153.6	3.279	0.0702
gtype:dtype	1	155.8	5.436	0.0197

```
hodg.cox2 |> drop1(test="Chisq")
```

Table 7.2.: Model summary table with dichotomized waiting time

	Df	AIC	LRT	$\Pr(>\text{Chi})$
	NA	149.0	NA	NA
score	1	168.6	21.604	0.0000
wt2	1	153.6	6.608	0.0102
gtype:dtype	1	152.0	4.970	0.0258

The new model has better (lower) AIC.

## 7.6. Checking for Outliers and Influential Observations

We will check for outliers using the deviance residuals. The martingale residuals show excess events or the opposite, but highly skewed, with the maximum possible value being 1, but the smallest value can be very large negative. Martingale residuals can detect unexpectedly long-lived patients, but patients who die unexpectedly early show up only in the deviance residual. Influence will be examined using dfbeta in a similar way to linear regression, logistic regression, or Poisson regression.

#### 7.6.1. Deviance Residuals

$$\begin{split} r_i^D &= \mathrm{sign}(r_i^M) \sqrt{-2 \left[r_i^M + \delta_i \ln(\delta_i - r_i^M)\right]} \\ r_i^D &= \mathrm{sign}(r_i^M) \sqrt{-2 \left[r_i^M + \delta_i \ln(r_i^{CS})\right]} \end{split}$$

Roughly centered on 0 with approximate standard deviation 1.

#### 7.6.2.

```
hodg.mart = residuals(hodg.cox2,type="martingale")
hodg.dev = residuals(hodg.cox2,type="deviance")
hodg.dfb = residuals(hodg.cox2,type="dfbeta")
hodg.preds = predict(hodg.cox2) #linear predictor

plot(hodg.preds,
    hodg.mart,
    xlab="Linear Predictor",
    ylab="Martingale Residual")
```



Figure 7.9.: Martingale Residuals vs. Linear Predictor

The smallest three martingale residuals in order are observations 1, 29,

and 18.

plot(hodg.preds,hodg.dev,xlab="Linear Predictor",ylab="Deviance Residual")



Figure 7.10.: Deviance Residuals vs. Linear Predictor

The two largest deviance residuals are observations 1 and 29. Worth examining.

#### 7.6.3. dfbeta

- dfbeta is the approximate change in the coefficient vector if that observation were dropped
- dfbetas is the approximate change in the coefficients, scaled by the standard error for the coefficients.

#### 7.6.3.1. Graft type

```
plot(hodg.dfb[,1],xlab="Observation Order",ylab="dfbeta for Graft Type")
```



Figure 7.11.: dfbeta Values by Observation Order for Graft Type

The smallest dfbeta for graft type is observation 1.

#### 7.6.3.2. Disease type

```
plot(hodg.dfb[,2],
     xlab="Observation Order",
     ylab="dfbeta for Disease Type")
```

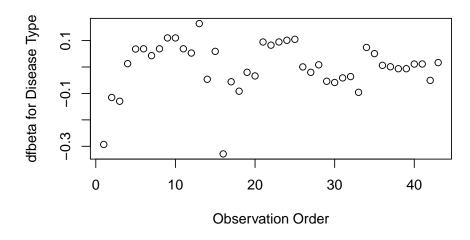


Figure 7.12.: dfbeta Values by Observation Order for Disease Type

The smallest two dfbeta values for disease type are observations 1 and 16.

## 7.6.3.3. Karnofsky score



Figure 7.13.: dfbeta Values by Observation Order for Karnofsky Score

The two highest dfbeta values for score are observations 1 and 18. The next three are observations 17, 29, and 19. The smallest value is observation 2.

### 7.6.3.4. Waiting time (dichotomized)

```
plot(
  hodg.dfb[,4],
  xlab="Observation Order",
  ylab="dfbeta for `Waiting Time < 80`")</pre>
```

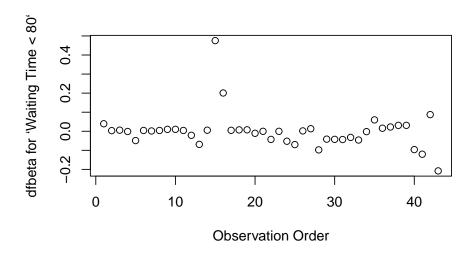


Figure 7.14.: dfbeta Values by Observation Order for Waiting Time (dichotomized)

The two large values of dfbeta for dichotomized waiting time are observations 15 and 16. This may have to do with the discretization of waiting time.

### 7.6.3.5. Interaction: graft type and disease type

```
plot(hodg.dfb[,5],
    xlab="Observation Order",
    ylab="dfbeta for dtype:gtype")
```



Figure 7.15.: dfbeta Values by Observation Order for dtype:gtype

The two largest values are observations 1 and 16. The smallest value is observation 35.

Table 7.3.: Observations to Examine by Residuals and Influence

Diagnostic	Observations to Examine
Martingale Residuals	1, 29, 18
Deviance Residuals	1, 29
Graft Type Influence	1
Disease Type Influence	1, 16
Karnofsky Score Influence	1, 18 (17, 29, 19)
Waiting Time Influence	15, 16
Graft by Disease Influence	1, 16, 35

The most important observations to examine seem to be 1, 15, 16, 18, and 29.

# 7.6.4.

# with(hodg,summary(time[delta==1]))

Min.	1st Qu.	Median	Mean	3rd Qu.	Max.
2	41.25	62.5	97.62	83.25	524

# with(hodg,summary(wtime))

Min.	1st Qu.	Median	Mean	3rd Qu.	Max.
5	16	24	37.7	55.5	171

# with(hodg,summary(score))

Min.	1st Qu.	Median	Mean	3rd Qu.	Max.
20	60	80	76.28	90	100

# hodg.cox2

### Call:

coxph(formula = Surv(time, event = delta == "dead") ~ gtype \*
 dtype + score + wt2, data = hodg2)

	coef	exp(coef)	se(coef)	Z	p
gtypeAutologous	0.67	1.94	0.59	1	0.263
dtypeHodgkins	2.33	10.25	0.73	3	0.002
score	-0.06	0.95	0.01	-4	8e-06
wt2long	-2.06	0.13	1.05	-2	0.050
gtypeAutologous:dtypeHodgkins	-2.07	0.13	0.93	-2	0.026

Likelihood ratio test=35 on 5 df, p=1e-06 n= 43, number of events= 26

```
hodg2[c(1,15,16,18,29),] |>
  select(gtype, dtype, time, delta, score, wtime) |>
  mutate(
    comment =
      c(
        "early death, good score, low risk",
        "high risk grp, long wait, poor score",
        "high risk grp, short wait, poor score",
        "early death, good score, med risk grp",
        "early death, good score, med risk grp"
    ))
```

gtype	dtype	time	delta	score	wtime	ecomment
Allogenic	Non-	28	dead	90	24	early death, good score,
	Hodgkins					low risk
Allogenic	Hodgkins	77	dead	60	102	high risk grp, long wait,
						poor score
Allogenic	Hodgkins	79	dead	70	71	high risk grp, short wait,
						poor score
Autologo	uNon-	53	dead	90	17	early death, good score,
	Hodgkins					med risk grp

gtype dt	ype t	ime	delta	score	wtime	comment
Autologouldo	odgkins	30	dead	90		early death, good score, med risk grp

### 7.6.5. Action Items

- Unusual points may need checking, particularly if the data are not completely cleaned. In this case, observations 15 and 16 may show some trouble with the dichotomization of waiting time, but it still may be useful.
- The two largest residuals seem to be due to unexpectedly early deaths, but unfortunately this can occur.
- If hazards don't look proportional, then we may need to use strata, between which the base hazards are permitted to be different. For this problem, the natural strata are the two diseases, because they could need to be managed differently anyway.
- A main point that we want to be sure of is the relative risk difference by disease type and graft type.

```
hodg.cox2 |>
  predict(
    reference = "zero",
    newdata = means |>
    mutate(
        wt2 = "short",
        score = 0),
    type = "lp") |>
  data.frame('linear predictor' = _) |>
  pander()
```

Table 7.8.: Linear Risk Predictors for Lymphoma

	linear.predictor
Non-Hodgkins, Allogenic	0
Non-	0.6651
Hodgkins, Autologous	
Hodgkins, Allogenic	2.327
Hodgkins, Autologous	0.9256

For Non-Hodgkin's, the allogenic graft is better. For Hodgkin's, the autologous graft is much better.

## 7.7. Stratified survival models

## 7.7.1. Revisiting the leukemia dataset (anderson)

We will analyze remission survival times on 42 leukemia patients, half on new treatment, half on standard treatment.

This is the same data as the drug6mp data from KMsurv, but with two other variables and without the pairing. This version comes from the Kleinbaum and Klein survival textbook (e.g., p281):

```
anderson =
  paste0(
    "http://web1.sph.emory.edu/dkleinb/allDatasets/",
    "surv2datasets/anderson.dta") |>
  haven::read_dta() |>
  mutate(
    status = status |>
        case_match(
```

```
1 ~ "relapse",
       0 ~ "censored"
      ),
    sex = sex |>
     case_match(
      0 ~ "female",
       1 ~ "male"
      ) |>
     factor() |>
     relevel(ref = "female"),
   rx = rx |>
     case_match(
      0 ~ "new",
       1 ~ "standard"
      ) |>
     factor() |> relevel(ref = "standard"),
   surv = Surv(
     time = survt,
     event = (status == "relapse"))
print(anderson)
```

## 7.7.2. Cox semi-parametric proportional hazards model

```
anderson.cox1 = coxph(
  formula = surv ~ rx + sex + logwbc,
  data = anderson)
```

```
summary(anderson.cox1)
Call:
coxph(formula = surv ~ rx + sex + logwbc, data = anderson)
 n= 42, number of events= 30
          coef exp(coef) se(coef)
                                      z Pr(>|z|)
rxnew
        -1.504
                   0.222
                            0.462 - 3.26
                                          0.0011 **
sexmale 0.315
                   1.370
                            0.455 0.69
                                          0.4887
logwbc
         1.682
                   5.376
                            0.337 5.00 5.8e-07 ***
Signif. codes: 0 '***' 0.001 '**' 0.05 '.' 0.1 ' ' 1
        exp(coef) exp(-coef) lower .95 upper .95
            0.222
                       4.498
                                 0.090
                                           0.549
rxnew
            1.370
                       0.730
                                 0.562
                                           3.338
sexmale
logwbc
            5.376
                       0.186
                                 2.779
                                          10.398
Concordance= 0.851 (se = 0.041)
Likelihood ratio test= 47.2 on 3 df,
                                        p=3e-10
                     = 33.5 \text{ on } 3 \text{ df},
                                        p=2e-07
Wald test
Score (logrank) test = 48 on 3 df, p=2e-10
```

### 7.7.2.1. Test the proportional hazards assumption

0.036 1 0.85

rx

```
cox.zph(anderson.cox1)

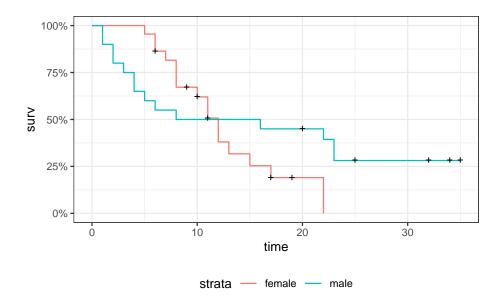
chisq df p
```

```
sex 5.420 1 0.02
logwbc 0.142 1 0.71
GLOBAL 5.879 3 0.12
```

# 7.7.2.2. Graph the K-M survival curves

```
anderson_km_model = survfit(
  formula = surv ~ sex,
  data = anderson)

anderson_km_model |>
  autoplot(conf.int = FALSE) +
  theme_bw() +
  theme(legend.position="bottom")
```



The survival curves cross, which indicates a problem in the proportionality assumption by sex.

### 7.7.3. Graph the Nelson-Aalen cumulative hazard

We can also look at the log-hazard ("cloglog survival") plots:

```
anderson_na_model = survfit(
  formula = surv ~ sex,
  data = anderson,
  type = "fleming")
anderson_na_model |>
  autoplot(
   fun = "cumhaz",
    conf.int = FALSE) +
  theme_classic() +
  theme(legend.position="bottom") +
  ylab("log(Cumulative Hazard)") +
  scale_y_continuous(
    trans = "log10",
    name = "Cumulative hazard (H(t), log scale)") +
  scale_x_continuous(
   breaks = c(1,2,5,10,20,50),
    trans = "log"
  )
```

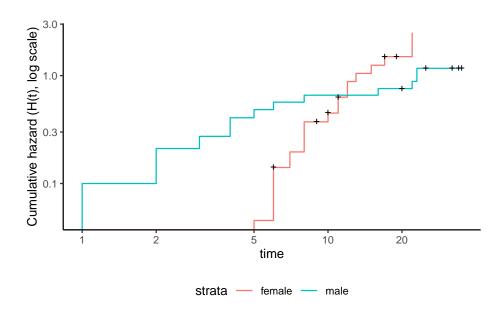


Figure 7.16.: Cumulative hazard (cloglog scale) for anderson data

This can be fixed by using strata or possibly by other model alterations.

### 7.7.4. The Stratified Cox Model

- In a stratified Cox model, each stratum, defined by one or more factors, has its own base survival function  $h_0(t)$ .
- But the coefficients for each variable not used in the strata definitions are assumed to be the same across strata.
- To check if this assumption is reasonable one can include interactions with strata and see if they are significant (this may generate a warning and NA lines but these can be ignored).
- Since the sex variable shows possible non-proportionality, we try stratifying on sex.

```
anderson.coxph.strat =
  coxph(
   formula =
      surv ~ rx + logwbc + strata(sex),
    data = anderson)
summary(anderson.coxph.strat)
Call:
coxph(formula = surv ~ rx + logwbc + strata(sex), data = anderson)
 n= 42, number of events= 30
         coef exp(coef) se(coef)
                                    z Pr(>|z|)
                 0.369
                          0.474 -2.11 0.035 *
rxnew -0.998
logwbc 1.454
                 4.279
                          0.344 4.22 2.4e-05 ***
---
Signif. codes: 0 '***' 0.001 '**' 0.05 '.' 0.1 ' ' 1
       exp(coef) exp(-coef) lower .95 upper .95
           0.369
                     2.713
                               0.146
                                          0.932
rxnew
logwbc
           4.279
                     0.234
                               2.180
                                          8.398
Concordance= 0.812 (se = 0.059)
Likelihood ratio test= 32.1 on 2 df,
                                       p=1e-07
Wald test
                    = 22.8 on 2 df,
                                       p=1e-05
Score (logrank) test = 30.8 on 2 df,
                                       p = 2e - 07
Let's compare this to a model fit only on the subset of males:
```

```
anderson.coxph.male =
  coxph(
```

```
formula = surv ~ rx + logwbc,
   subset = sex == "male",
   data = anderson)
summary(anderson.coxph.male)
Call:
coxph(formula = surv ~ rx + logwbc, data = anderson, subset = sex ==
    "male")
 n= 20, number of events= 14
        coef exp(coef) se(coef) z Pr(>|z|)
                 0.138
                          0.739 -2.68 0.0075 **
rxnew -1.978
logwbc 1.743
                 5.713
                          0.536 3.25
                                      0.0011 **
Signif. codes: 0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
       exp(coef) exp(-coef) lower .95 upper .95
                     7.227
rxnew
          0.138
                              0.0325
                                        0.589
          5.713
                     0.175
                              1.9991
                                        16.328
logwbc
Concordance= 0.905 (se = 0.043)
Likelihood ratio test= 29.2 on 2 df,
                                       p=5e-07
Wald test
                    = 15.3 on 2 df,
                                       p=5e-04
Score (logrank) test = 26.4 on 2 df,
                                       p=2e-06
anderson.coxph.female =
  coxph(
   formula =
     surv ~ rx + logwbc,
   subset = sex == "female",
```

```
data = anderson)
summary(anderson.coxph.female)
Call:
coxph(formula = surv ~ rx + logwbc, data = anderson, subset = sex ==
    "female")
 n= 22, number of events= 16
                                     z Pr(>|z|)
         coef exp(coef) se(coef)
rxnew -0.311
                  0.733
                           0.564 - 0.55
                                          0.581
logwbc 1.206
                  3.341
                           0.503 2.40
                                          0.017 *
Signif. codes: 0 '***' 0.001 '**' 0.05 '.' 0.1 ' ' 1
       exp(coef) exp(-coef) lower .95 upper .95
rxnew
           0.733
                      1.365
                                0.243
                                           2.21
           3.341
                      0.299
                                1.245
                                           8.96
logwbc
Concordance= 0.692 (se = 0.085)
Likelihood ratio test= 6.65 on 2 df,
                                        p=0.04
Wald test
                     = 6.36 on 2 df,
                                        p=0.04
Score (logrank) test = 6.74 on 2 df,
                                        p=0.03
The coefficients of treatment look different. Are they statistically differ-
ent?
anderson.coxph.strat.intxn =
  coxph(
   formula = surv ~ strata(sex) * (rx + logwbc),
```

data = anderson)

```
anderson.coxph.strat.intxn |> summary()
Call:
coxph(formula = surv ~ strata(sex) * (rx + logwbc), data = anderson)
 n= 42, number of events= 30
                        coef exp(coef) se(coef)
                                                    z Pr(>|z|)
rxnew
                      -0.311
                                 0.733
                                          0.564 - 0.55
                                                         0.581
                                          0.503 2.40
logwbc
                       1.206
                                 3.341
                                                         0.017 *
strata(sex)male:rxnew -1.667
                                 0.189
                                          0.930 - 1.79
                                                         0.073 .
strata(sex)male:logwbc 0.537
                                 1.710
                                          0.735 0.73
                                                         0.465
Signif. codes: 0 '***' 0.001 '**' 0.05 '.' 0.1 ' ' 1
                      exp(coef) exp(-coef) lower .95 upper .95
                                     1.365
                                                          2.21
rxnew
                          0.733
                                              0.2427
logwbc
                          3.341
                                     0.299
                                              1.2452
                                                          8.96
strata(sex)male:rxnew
                          0.189
                                     5.294
                                              0.0305
                                                          1.17
strata(sex)male:logwbc
                          1.710
                                     0.585
                                              0.4048
                                                          7.23
Concordance= 0.797 (se = 0.058)
Likelihood ratio test= 35.8 on 4 df,
                                       p = 3e - 07
Wald test
                    = 21.7 on 4 df,
                                       p = 2e - 04
Score (logrank) test = 33.1 on 4 df,
                                       p=1e-06
anova(
  anderson.coxph.strat.intxn,
  anderson.coxph.strat)
```

loglik	Chisq	Df	$\Pr(> \text{Chi} )$
-53.85	NA	NA	NA
-55.73	3.766	2	0.1521

We don't have enough evidence to tell the difference between these two models.

### 7.7.5. Conclusions

- We chose to use a stratified model because of the apparent nonproportionality of the hazard for the sex variable.
- When we fit interactions with the strata variable, we did not get an improved model (via the likelihood ratio test).
- So we use the stratifed model with coefficients that are the same across strata.

## 7.7.6. Another Modeling Approach

- We used an additive model without interactions and saw that we might need to stratify by sex.
- Instead, we could try to improve the model's functional form maybe the interaction of treatment and sex is real, and after fitting that we might not need separate hazard functions.
- Either approach may work.

```
anderson.coxph.intxn =
  coxph(
   formula = surv ~ (rx + logwbc) * sex,
   data = anderson)

anderson.coxph.intxn |> summary()
```

```
Call:
coxph(formula = surv ~ (rx + logwbc) * sex, data = anderson)
 n= 42, number of events= 30
                  coef exp(coef) se(coef)
                                             z Pr(>|z|)
rxnew
               -0.3748
                          0.6874
                                  0.5545 - 0.68
                                                   0.499
                          2.8971
logwbc
                1.0637
                                  0.4726 2.25
                                                   0.024 *
sexmale
               -2.8052
                          0.0605
                                  2.0323 -1.38
                                                   0.167
                                                   0.017 *
rxnew:sexmale
              -2.1782
                          0.1132
                                  0.9109 - 2.39
logwbc:sexmale 1.2303
                          3.4223
                                  0.6301 1.95
                                                  0.051 .
Signif. codes: 0 '***' 0.001 '**' 0.05 '.' 0.1 ' ' 1
               exp(coef) exp(-coef) lower .95 upper .95
                  0.6874
                             1.455
                                      0.23185
                                                  2.038
rxnew
                  2.8971
                             0.345
                                      1.14730
                                                  7.315
logwbc
sexmale
                  0.0605
                             16.531
                                      0.00113
                                                  3.248
rxnew:sexmale
                  0.1132
                             8.830
                                      0.01899
                                                  0.675
logwbc:sexmale
                  3.4223
                             0.292
                                      0.99539
                                                 11.766
Concordance= 0.861 (se = 0.036)
Likelihood ratio test= 57 on 5 df,
                                     p=5e-11
                     = 35.6 on 5 df,
Wald test
                                       p=1e-06
Score (logrank) test = 57.1 on 5 df,
                                       p=5e-11
cox.zph(anderson.coxph.intxn)
```

```
chisq df p
rx 0.136 1 0.71
logwbc 1.652 1 0.20
sex 1.266 1 0.26
rx:sex 0.149 1 0.70
```

```
logwbc:sex 0.102 1 0.75
GLOBAL
           3.747
                  5 0.59
```

# load the data:

# 7.8. Time-varying covariates

(adapted from Klein, Moeschberger, et al. (2003), §9.2)

## 7.8.1. Motivating example: back to the leukemia dataset

```
data(bmt, package = 'KMsurv')
bmt |> as_tibble() |> print(n = 5)
# A tibble: 137 x 22
 group
       t1
            t2
                d1
                    d2
                         d3
                             ta
                                 da
                                     tc
                                          dc
                                              tp
                                                  dp
 2081
    1
          2081
                 0
                     0
                         0
                             67
                                  1
                                     121
                                          1
                                              13
```

z1

```
1
         1433
               1433
                         0
                               0
                                        1433
                                                  0
                                                      236
                                                              1
                                                                    12
# i 132 more rows
# i 9 more variables: z2 <int>, z3 <int>, z4 <int>, z5 <int>, z6 <int>,
    z7 <int>, z8 <int>, z9 <int>, z10 <int>
```

This dataset comes from the Copelan et al. (1991) study of allogenic bone marrow transplant therapy for acute myeloid leukemia (AML) and acute lymphoblastic leukemia (ALL).

### **Outcomes (endpoints)**

• The main endpoint is disease-free survival (t2 and d3) for the three risk groups, "ALL", "AML Low Risk", and "AML High Risk".

#### Possible intermediate events

- graft vs. host disease (**GVHD**), an immunological rejection response to the transplant (bad)
- acute (AGVHD)
- chronic (CGVHD)
- platelet recovery, a return of platelet count to normal levels (good)

One or the other, both in either order, or neither may occur.

### **Covariates**

- We are interested in possibly using the covariates z1-z10 to adjust for other factors.
- In addition, the time-varying covariates for acute GVHD, chronic GVHD, and platelet recovery may be useful.

### 7.8.1.1. Preprocessing

We reformat the data before analysis:

```
# reformat the data:
bmt1 =
  bmt |>
  as_tibble() |>
  mutate(
   id = 1:n(), # will be used to connect multiple records for the same individual
```

```
group = group |>
 case_match(
   1 ~ "ALL",
   2 ~ "Low Risk AML",
   3 ~ "High Risk AML") |>
 factor(levels = c("ALL", "Low Risk AML", "High Risk AML")),
`patient age` = z1,
`donor age` = z2,
\epsilon = z3 >
 case_match(
   0 ~ "Female",
   1 ~ "Male"),
donor sex = z4 >
 case_match(
   0 ~ "Female",
   1 ~ "Male"),
`Patient CMV Status` = z5 |>
 case_match(
   0 ~ "CMV Negative",
   1 ~ "CMV Positive"),
`Donor CMV Status` = z6 |>
 case_match(
   0 ~ "CMV Negative",
   1 ~ "CMV Positive"),
'Waiting Time to Transplant' = z7,
```

```
FAB = z8 \mid >
      case_match(
       1 ~ "Grade 4 Or 5 (AML only)",
       0 ~ "Other") |>
     factor() |>
     relevel(ref = "Other"),
   hospital = z9 |> # `z9` is hospital
      case_match(
       1 ~ "Ohio State University",
       2 ~ "Alferd",
        3 ~ "St. Vincent",
        4 ~ "Hahnemann") |>
      factor() |>
      relevel(ref = "Ohio State University"),
   MTX = (z10 == 1) # a prophylatic treatment for GVHD
 ) |>
  select(-(z1:z10)) # don't need these anymore
bmt1 |>
  select(group, id:MTX) |>
 print(n = 10)
# A tibble: 137 x 12
            id `patient age` `donor age` `patient sex` `donor sex`
  group
   <fct> <int>
                                   <int> <chr>
                       <int>
                                                       <chr>
 1 ALL
                          26
                                      33 Male
                                                       Female
           1
 2 ALL
             2
                          21
                                      37 Male
                                                       Male
 3 ALL
           3
                          26
                                      35 Male
                                                       Male
 4 ALL
           4
                          17
                                      21 Female
                                                       Male
           5
 5 ALL
                          32
                                      36 Male
                                                       Male
```

6	ALL	6	22	31 Male	Male
7	ALL	7	20	17 Male	Female
8	ALL	8	22	24 Male	Female
9	ALL	9	18	21 Female	Male
10	ALL	10	24	40 Male	Male

<sup>#</sup> i 127 more rows

- # i 6 more variables: `Patient CMV Status` <chr>, `Donor CMV Status` <chr>,
- # `Waiting Time to Transplant` <int>, FAB <fct>, hospital <fct>, MTX <lgl>

### 7.8.2. Time-Dependent Covariates

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

### 7.8.3. Analysis in R

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

```
bmt2 = bmt1 |>
    #set up new long-format data set:
    tmerge(bmt1, id = id, tstop = t2) |>

# the following three steps can be in any order,
# and will still produce the same result:
#add aghvd as tdc:
    tmerge(bmt1, id = id, agvhd = tdc(ta)) |>
    #add cghvd as tdc:
    tmerge(bmt1, id = id, cgvhd = tdc(tc)) |>
    #add platelet recovery as tdc:
    tmerge(bmt1, id = id, precovery = tdc(tp))

bmt2 = bmt2 |>
    as_tibble() |>
    mutate(status = as.numeric((tstop == t2) & d3))
# status only = 1 if at end of t2 and not censored
```

Let's see how we've rearranged the first row of the data:

```
bmt1 |>
  dplyr::filter(id == 1) |>
  dplyr::select(id, t1, d1, t2, d2, d3, ta, da, tc, dc, tp, dp)
     id
           t1
               d1
                     d2
                             d3
                                      da
                                                        dp
                                  ta
                                            tc
                                               dc
                                                    tp
     1
         2081
                   2081
                          0
                                          121
                               0
                                  67
                                                    13
                                                         1
                                       1
                                                 1
```

The event times for this individual are:

- t = 0 time of transplant
- tp = 13 platelet recovery

- ta = 67 acute GVHD onset
- tc = 121 chronic GVHD onset
- t2 = 2081 end of study, patient not relapsed or dead

After converting the data to long-format, we have:

```
bmt2 |>
    select(
    id,
    tstart,
    tstop,
    agvhd,
    cgvhd,
    precovery,
    status
) |>
    dplyr::filter(id == 1)
```

id	tstart	tstop	agvhd	cgvhd	precovery	status
1	0	13	0	0	0	0
1	13	67	0	0	1	0
1	67	121	1	0	1	0
1	121	2081	1	1	1	0

Note that status could have been 1 on the last row, indicating that relapse or death occurred; since it is false, the participant must have exited the study without experiencing relapse or death (i.e., they were censored).

# 7.8.4. Event sequences

Let:

- A = acute GVHD
- C = chronic GVHD
- P = platelet recovery

Each of the eight possible combinations of A or not-A, with C or not-C, with P or not-P occurs in this data set.

- A always occurs before C, and P always occurs before C, if both occur.
- Thus there are ten event sequences in the data set: None, A, C, P, AC, AP, PA, PC, APC, and PAC.
- In general, there could be as many as 1+3+(3)(2)+6=16 sequences, but our domain knowledge tells us that some are missing: CA, CP, CAP, CPA, PCA, PC, PAC
- Different subjects could have 1, 2, 3, or 4 intervals, depending on which of acute GVHD, chronic GVHD, and/or platelet recovery occurred.
- The final interval for any subject has status = 1 if the subject relapsed or died at that time; otherwise status = 0.
- Any earlier intervals have status = 0.
- Even though there might be multiple lines per ID in the dataset, there is never more than one event, so no alterations need be made in the estimation procedures or in the interpretation of the output.
- The function tmerge in the survival package eases the process of constructing the new long-format dataset.

### 7.8.5. Model with Time-Fixed Covariates

```
bmt1 =
  bmt1 |>
  mutate(surv = Surv(t2,d3))
```

```
bmt_coxph_TF = coxph(
 formula = surv ~ group + `patient age`*`donor age` + FAB,
 data = bmt1)
summary(bmt coxph TF)
Call:
coxph(formula = surv ~ group + `patient age` * `donor age` +
   FAB, data = bmt1)
 n= 137, number of events= 83
                                coef exp(coef)
                                                se(coef)
                                                             z Pr(>|z|)
groupLow Risk AML
                           -1.090648 0.335999
                                                0.354279 -3.08 0.00208 **
groupHigh Risk AML
                           -0.403905 0.667707
                                                0.362777 -1.11 0.26555
`patient age`
                           -0.081639  0.921605  0.036107  -2.26  0.02376 *
`donor age`
                           -0.084587   0.918892   0.030097   -2.81   0.00495 **
FABGrade 4 Or 5 (AML only) 0.837416 2.310388 0.278464 3.01 0.00264 **
`patient age`: `donor age`
                            0.003159 1.003164 0.000951 3.32 0.00089 ***
Signif. codes: 0 '*** 0.001 '** 0.01 '* 0.05 '.' 0.1 ' ' 1
                           exp(coef) exp(-coef) lower .95 upper .95
groupLow Risk AML
                               0.336
                                          2.976
                                                    0.168
                                                              0.673
groupHigh Risk AML
                               0.668
                                          1.498
                                                    0.328
                                                              1.360
`patient age`
                               0.922
                                          1.085
                                                    0.859
                                                              0.989
`donor age`
                                                    0.866
                               0.919
                                          1.088
                                                              0.975
FABGrade 4 Or 5 (AML only)
                               2.310
                                          0.433
                                                    1.339
                                                              3.988
`patient age`:`donor age`
                               1.003
                                          0.997
                                                    1.001
                                                              1.005
Concordance= 0.665 (se = 0.033)
Likelihood ratio test= 32.8 on 6 df,
                                        p=1e-05
                     = 33 on 6 df,
Wald test
                                      p=1e-05
Score (logrank) test = 35.8 on 6 df,
                                        p = 3e - 06
```

## drop1(bmt\_coxph\_TF, test = "Chisq")

	Df	AIC	LRT	Pr(>Chi)
	NA	725.8	NA	NA
group	2	734.3	12.511	0.0019
FAB	1	733.0	9.216	0.0024
patient age:donor age	1	733.3	9.514	0.0020

```
bmt1$mres =
  bmt_coxph_TF |>
  update(. ~ . - `donor age`) |>
  residuals(type="martingale")

bmt1 |>
  ggplot(aes(x = `donor age`, y = mres)) +
  geom_point() +
  geom_smooth(method = "loess", aes(col = "loess")) +
  geom_smooth(method = 'lm', aes(col = "lm")) +
  theme_classic() +
  xlab("Donor age") +
  ylab("Martingale Residuals") +
  guides(col=guide_legend(title = ""))
```

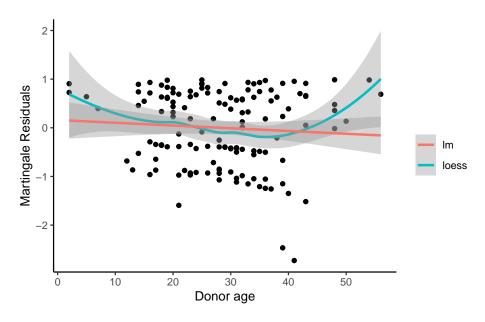


Figure 7.17.: Martingale residuals for Donor age

A more complex functional form for donor age seems warranted; left as an exercise for the reader.

Now we will add the time-varying covariates:

```
# add counting process formulation of Surv():
bmt2 =
  bmt2 |>
  mutate(
    surv =
    Surv(
      time = tstart,
      time2 = tstop,
```

```
event = status,
type = "counting"))
```

Let's see how the data looks for patient 15:

```
bmt1 |> dplyr::filter(id == 15) |> dplyr::select(tp, dp, tc,dc, ta, da, FAB, surv, t

tp dp tc dc ta da FAB surv t1 d1 t2 d2 d3
```

$\operatorname{tp}$	dр	$\operatorname{tc}$	dc	ta	da	FAB	surv	t1	dI	t2	d2	d3
21	1	220	1	418	0	Other	418	418	1	418	0	1

```
bmt2 |> dplyr::filter(id == 15) |> dplyr::select(id, agvhd, cgvhd, precovery, surv)
```

id	agvhd	cgvhd	precovery	surv
15	0	0	0	(0, 21+]
15	0	0	1	(21,220+]
15	0	1	1	(220,418]

# 7.8.6. Model with Time-Dependent Covariates

```
bmt_coxph_TV = coxph(
  formula =
    surv ~
    group + `patient age`*`donor age` + FAB + agvhd + cgvhd + precovery,
    data = bmt2)
summary(bmt_coxph_TV)
```

Call:

```
coxph(formula = surv ~ group + `patient age` * `donor age` +
   FAB + agvhd + cgvhd + precovery, data = bmt2)
 n= 341, number of events= 83
                                coef exp(coef)
                                                se(coef)
                                                            z Pr(>|z|)
groupLow Risk AML
                           -1.038514 0.353980 0.358220 -2.90
                                                                 0.0037 **
                                                                 0.3101
groupHigh Risk AML
                           -0.380481 0.683533 0.374867 -1.01
`patient age`
                           -0.073351 0.929275 0.035956 -2.04
                                                                 0.0413 *
`donor age`
                           -0.076406 0.926440 0.030196 -2.53
                                                                 0.0114 *
FABGrade 4 Or 5 (AML only) 0.805700 2.238263 0.284273 2.83
                                                                 0.0046 **
                           0.150565 1.162491 0.306848 0.49
                                                                 0.6237
agvhd
cgvhd
                           -0.116136  0.890354  0.289046  -0.40
                                                                 0.6878
precovery
                           -0.941123 0.390190 0.347861 -2.71
                                                                 0.0068 **
`patient age`:`donor age`
                           0.002895 1.002899 0.000944 3.07
                                                                 0.0022 **
Signif. codes: 0 '***' 0.001 '**' 0.05 '.' 0.1 ' ' 1
                           exp(coef) exp(-coef) lower .95 upper .95
                               0.354
                                          2.825
                                                   0.175
groupLow Risk AML
                                                              0.714
groupHigh Risk AML
                               0.684
                                          1.463
                                                   0.328
                                                              1.425
`patient age`
                               0.929
                                          1.076
                                                   0.866
                                                              0.997
`donor age`
                               0.926
                                          1.079
                                                   0.873
                                                              0.983
FABGrade 4 Or 5 (AML only)
                               2.238
                                          0.447
                                                   1.282
                                                              3.907
                                          0.860
                                                   0.637
                                                              2.121
agvhd
                               1.162
                               0.890
                                                   0.505
cgvhd
                                          1.123
                                                              1.569
precovery
                               0.390
                                          2.563
                                                   0.197
                                                              0.772
`patient age`: `donor age`
                               1.003
                                          0.997
                                                   1.001
                                                              1.005
Concordance= 0.702 (se = 0.028)
Likelihood ratio test= 40.3 on 9 df,
                                        p = 7e - 06
Wald test
                     = 42.4
                            on 9 df,
                                        p = 3e - 06
Score (logrank) test = 47.2
                                        p=4e-07
                            on 9 df,
```

Platelet recovery is highly significant.

Neither acute GVHD (agvhd) nor chronic GVHD (cgvhd) has a statistically significant effect here, nor are they significant in models with the other one removed.

```
update(bmt_coxph_TV, .~.-agvhd) |> summary()
Call:
coxph(formula = surv ~ group + `patient age` + `donor age` +
   FAB + cgvhd + precovery + `patient age`: `donor age`, data = bmt2)
 n= 341, number of events= 83
                                coef exp(coef)
                                                se(coef)
                                                             z Pr(>|z|)
groupLow Risk AML
                           -1.049870 0.349983
                                                0.356727 -2.94
                                                                  0.0032 **
                           -0.417049 0.658988
                                                                  0.2537
groupHigh Risk AML
                                                0.365348 - 1.14
`patient age`
                           -0.070749 0.931696 0.035477 -1.99
                                                                  0.0461 *
`donor age`
                           -0.075693 0.927101 0.030075 -2.52
                                                                 0.0118 *
FABGrade 4 Or 5 (AML only) 0.807035 2.241253 0.283437 2.85
                                                                 0.0044 **
                           -0.095393 0.909015 0.285979 -0.33
                                                                 0.7387
cgvhd
precovery
                           -0.983653 0.373942 0.338170 -2.91
                                                                 0.0036 **
`patient age`: `donor age`
                            0.002859 1.002863 0.000936 3.05
                                                                 0.0023 **
Signif. codes: 0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
                           exp(coef) exp(-coef) lower .95 upper .95
groupLow Risk AML
                               0.350
                                          2.857
                                                    0.174
                                                              0.704
groupHigh Risk AML
                               0.659
                                          1.517
                                                    0.322
                                                              1.349
`patient age`
                                                              0.999
                               0.932
                                          1.073
                                                    0.869
`donor age`
                               0.927
                                          1.079
                                                    0.874
                                                              0.983
FABGrade 4 Or 5 (AML only)
                               2.241
                                          0.446
                                                    1.286
                                                              3.906
cgvhd
                               0.909
                                          1.100
                                                    0.519
                                                              1.592
precovery
                               0.374
                                          2.674
                                                    0.193
                                                              0.726
```

```
`patient age`: `donor age`
                               1.003
                                          0.997
                                                    1.001
                                                              1.005
Concordance= 0.701 (se = 0.027)
Likelihood ratio test= 40 on 8 df,
                                      p = 3e - 06
Wald test
                     = 42.4 on 8 df,
                                        p=1e-06
Score (logrank) test = 47.2 on 8 df,
                                        p=1e-07
update(bmt_coxph_TV, .~.-cgvhd) |> summary()
Call:
coxph(formula = surv ~ group + `patient age` + `donor age` +
   FAB + agvhd + precovery + `patient age`: `donor age`, data = bmt2)
 n= 341, number of events= 83
                                coef exp(coef)
                                                se(coef)
                                                             z Pr(>|z|)
groupLow Risk AML
                           -1.019638 0.360725
                                                0.355311 -2.87
                                                                 0.0041 **
                           -0.381356  0.682935  0.374568 -1.02
                                                                 0.3086
groupHigh Risk AML
`patient age`
                           -0.073189 0.929426 0.035890 -2.04
                                                                 0.0414 *
                           -0.076753 0.926118 0.030121 -2.55
`donor age`
                                                                 0.0108 *
FABGrade 4 Or 5 (AML only) 0.811716 2.251769
                                                0.284012 2.86
                                                                 0.0043 **
agvhd
                            0.131621 1.140676 0.302623 0.43
                                                                 0.6636
                           -0.946697  0.388021  0.347265  -2.73
                                                                 0.0064 **
precovery
`patient age`:`donor age`
                           0.002904 1.002908 0.000943 3.08
                                                                 0.0021 **
Signif. codes: 0 '***' 0.001 '**' 0.05 '.' 0.1 ' ' 1
                           exp(coef) exp(-coef) lower .95 upper .95
                                                    0.180
groupLow Risk AML
                               0.361
                                          2.772
                                                              0.724
groupHigh Risk AML
                               0.683
                                          1.464
                                                    0.328
                                                              1.423
`patient age`
                               0.929
                                          1.076
                                                    0.866
                                                              0.997
`donor age`
                               0.926
                                          1.080
                                                    0.873
                                                              0.982
FABGrade 4 Or 5 (AML only)
                               2.252
                                          0.444
                                                    1.291
                                                              3.929
```

```
agvhd
                               1.141
                                         0.877
                                                   0.630
                                                             2.064
precovery
                               0.388
                                         2.577
                                                    0.196
                                                             0.766
`patient age`:`donor age`
                               1.003
                                         0.997
                                                    1.001
                                                             1.005
Concordance= 0.701 (se = 0.027)
Likelihood ratio test= 40.1 on 8 df,
                                       p = 3e - 06
Wald test
                     = 42.1
                            on 8 df,
                                        p=1e-06
Score (logrank) test = 47.1 on 8 df,
                                       p=1e-07
Let's drop them both:
bmt_coxph_TV2 = update(bmt_coxph_TV, . ~ . - agvhd -cgvhd)
bmt coxph TV2 |> summary()
Call:
coxph(formula = surv ~ group + `patient age` + `donor age` +
    FAB + precovery + `patient age`: `donor age`, data = bmt2)
 n= 341, number of events= 83
                                coef exp(coef) se(coef)
                                                            z Pr(>|z|)
                          -1.032520 0.356108 0.353202 -2.92
groupLow Risk AML
                                                                0.0035 **
groupHigh Risk AML
                           -0.413888 0.661075 0.365209 -1.13
                                                                 0.2571
`patient age`
                           -0.070965 0.931495 0.035453 -2.00
                                                                 0.0453 *
`donor age`
                           -0.076052 0.926768 0.030007 -2.53
                                                                0.0113 *
FABGrade 4 Or 5 (AML only) 0.811926 2.252242 0.283231 2.87
                                                                0.0041 **
precovery
                           -0.983505 0.373998 0.337997 -2.91
                                                                 0.0036 **
                           0.002872 1.002876 0.000936 3.07
                                                                0.0021 **
`patient age`: `donor age`
Signif. codes: 0 '***' 0.001 '**' 0.05 '.' 0.1 ' ' 1
                           exp(coef) exp(-coef) lower .95 upper .95
groupLow Risk AML
                               0.356
                                         2.808
                                                   0.178
                                                             0.712
```

groupHigh Risk AML	0.661	1.513	0.323	1.352		
`patient age`	0.931	1.074	0.869	0.999		
`donor age`	0.927	1.079	0.874	0.983		
FABGrade 4 Or 5 (AML only)	2.252	0.444	1.293	3.924		
precovery	0.374	2.674	0.193	0.725		
`patient age`:`donor age`	1.003	0.997	1.001	1.005		
Concordance= 0.7 (se = 0.027	')					
Likelihood ratio test= 39.9	on 7 df,	p=1e-06				
Wald test = 42.2	on 7 df,	p=5e-07				
Score (logrank) test = 47.1 on 7 df, p=5e-08						

## 7.9. Recurrent Events

(Adapted from Kleinbaum and Klein, Ch 8)

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

### 7.9.1. Bladder Cancer Data Set

The bladder cancer dataset from Kleinbaum and Klein contains recurrent event outcome information for eighty-six cancer patients followed for the recurrence of bladder cancer tumor after transurethral surgical excision (Byar and Green 1980). The exposure of interest is the effect of the drug

treatment of thiotepa. Control variables are the initial number and initial size of tumors. The data layout is suitable for a counting processes approach.

This drug is still a possible choice for some patients. Another therapeutic choice is Bacillus Calmette-Guerin (BCG), a live bacterium related to cow tuberculosis.

## 7.9.1.1. Data dictionary

Table 7.15.: Variables in the bladder dataset

Variable	Definition
id	Patient unique ID
status	for each time interval: $1 = \text{recurred}$ , $0 = \text{censored}$
interval	1 = first recurrence, etc.
intime	'tstop - tstart (all times in months)
tstart	start of interval
tstop	end of interval
tx	treatment code, $1 = \text{thiotepa}$
num	number of initial tumors
size	size of initial tumors (cm)

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

## 7.9.1.2. Different intervals for the same patient are correlated.

- Is the effective sample size 47 or 112? This might narrow confidence intervals by as much as a factor of  $\sqrt{112/47} = 1.54$
- What happens if I have 5 treatment and 5 control values and want to do a t-test and I then duplicate the 10 values as if the sample size was 20? This falsely narrows confidence intervals by a factor of  $\sqrt{2} = 1.41$ .

```
bladder =
  paste0(
    "http://web1.sph.emory.edu/dkleinb/allDatasets",
    "/surv2datasets/bladder.dta") |>
  read_dta() |>
  as_tibble()

bladder = bladder[-1,] #remove subject with 0 observation time
print(bladder)
```

```
bladder =
  bladder |>
  mutate(
    surv =
        Surv(
        time = start,
        time2 = stop,
        event = event,
        type = "counting"))

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

```
#results with biased variance-covariance matrix:
summary(bladder.cox1)
Call:
coxph(formula = surv ~ tx + num + size, data = bladder)
 n= 190, number of events= 112
        coef exp(coef) se(coef)
                                   z Pr(>|z|)
tx
     -0.4116
                0.6626
                         0.1999 -2.06 0.03947 *
      0.1637
                1.1778
                         0.0478 3.43 0.00061 ***
num
size -0.0411
                0.9598
                         0.0703 -0.58 0.55897
---
Signif. codes: 0 '***' 0.001 '**' 0.05 '.' 0.1 ' ' 1
     exp(coef) exp(-coef) lower .95 upper .95
                    1.509
tx
         0.663
                              0.448
                                         0.98
         1.178
                    0.849
                              1.073
                                         1.29
num
         0.960
                    1.042
                              0.836
                                         1.10
size
Concordance= 0.624 (se = 0.032)
Likelihood ratio test= 14.7
                            on 3 df,
                                        p=0.002
Wald test
                    = 15.9
                            on 3 df,
                                        p=0.001
Score (logrank) test = 16.2 on 3 df,
                                        p=0.001
```

### Note

The likelihood ratio and score tests assume independence of observations within a cluster. The Wald and robust score tests do not.

## 7.9.1.3. adding cluster = id

If we add cluster= id to the call to coxph, the coefficient estimates don't change, but we get an additional column in the summary() output: robust se:

```
bladder.cox2 = coxph(
  formula = surv ~ tx + num + size,
  cluster = id,
  data = bladder)
#unbiased though this reduces power:
summary(bladder.cox2)
Call:
coxph(formula = surv ~ tx + num + size, data = bladder, cluster = id)
 n= 190, number of events= 112
        coef exp(coef) se(coef) robust se
                                               z Pr(>|z|)
     -0.4116
                0.6626
                         0.1999
                                   0.2488 - 1.65
                                                   0.0980 .
tx
      0.1637
                1.1778
num
                         0.0478
                                   0.0584 2.80
                                                   0.0051 **
                0.9598
size -0.0411
                         0.0703
                                   0.0742 - 0.55
                                                   0.5799
Signif. codes: 0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
     exp(coef) exp(-coef) lower .95 upper .95
                    1.509
                                          1.08
tx
         0.663
                              0.407
         1.178
                    0.849
                                          1.32
                              1.050
num
         0.960
size
                    1.042
                              0.830
                                          1.11
Concordance= 0.624 (se = 0.031)
Likelihood ratio test= 14.7 on 3 df,
                                         p=0.002
```

```
Wald test = 11.2 on 3 df, p=0.01
Score (logrank) test = 16.2 on 3 df, p=0.001, Robust = 10.8 p=0.01
```

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

robust se is larger than se, and accounts for the repeated observations from the same individuals:

## round(bladder.cox2\$naive.var, 4)

0.0400	-0.0014	0.0000
-0.0014	0.0023	0.0007
0.0000	0.0007	0.0049

### round(bladder.cox2\$var, 4)

0.0619	-0.0026	-0.0004
-0.0026	0.0034	0.0013
-0.0004	0.0013	0.0055

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

```
with(bladder.cox2, diag(var)/diag(naive.var)) |> sqrt()
```

[1] 1.244 1.223 1.056

We might try dropping the non-significant size variable:

```
#remove non-significant size variable:
bladder.cox3 = bladder.cox2 |> update(. ~ . - size)
summary(bladder.cox3)
Call:
coxph(formula = surv ~ tx + num, data = bladder, cluster = id)
 n= 190, number of events= 112
       coef exp(coef) se(coef) robust se
                                             z Pr(>|z|)
              0.6625
                       0.2003
tx -0.4117
                                 0.2515 - 1.64
                                                 0.1017
num 0.1700
              1.1853
                        0.0465
                                 0.0564 3.02
                                                 0.0026 **
Signif. codes: 0 '***' 0.001 '**' 0.05 '.' 0.1 ' ' 1
   exp(coef) exp(-coef) lower .95 upper .95
tx
       0.663
                  1.509
                            0.405
                                        1.08
        1.185
                  0.844
                             1.061
                                        1.32
num
Concordance= 0.623 (se = 0.031)
Likelihood ratio test= 14.3 on 2 df,
                                        p=8e-04
Wald test
                    = 10.2 on 2 df,
                                        p=0.006
Score (logrank) test = 15.8 on 2 df,
                                        p=4e-04,
                                                  Robust = 10.6 p=0.005
  (Note: the likelihood ratio and score tests assume independence of
```

observations within a cluster, the Wald and robust score tests do not).

Ways to check PH assumption:

- cloglog
- schoenfeld residuals
- interaction with time

# 7.10. Age as the time scale

See Canchola et al. (2003).

## Configuring R

Functions from these packages will be used throughout this document:

```
library(pander) # format tables for markdown
library(ggplot2) # graphics
library(ggeasy) # help with graphics
library(dplyr) # manipulate data
library(haven) # import Stata files
library(knitr) # format R output for markdown
library(tidyr) # Tools to help to create tidy data
library(plotly) # interactive graphics
library(dobson) # datasets from Dobson and Barnett 2018
library(parameters) # format model output tables for markdown
library(conflicted) # check for conflicting function definitions
conflicts_prefer(dplyr::filter)
```

Here are some R settings I use in this document:

```
rm(list = ls()) # delete any data that's already loaded into R
knitr::opts_chunk$set(message = FALSE)
pander::panderOptions("table.emphasize.rownames", FALSE)
options('digits' = 4)
```

## 8.1. Parametric Survival Models

## 8.1.1. Exponential Distribution

• The exponential distribution is the basic distribution for survival analysis.

$$\begin{split} f(t) &= \lambda e^{-\lambda t} \\ \log \left\{ f(t) \right\} &= \log \left\{ \lambda \right\} - \lambda t \\ F(t) &= 1 - e^{-\lambda t} \\ S(t) &= e^{-\lambda t} \\ H(t) &= \log \left\{ S(t) \right\} = -\lambda t \\ h(t) &= \lambda \\ \mathrm{E}(T) &= \lambda^{-1} \end{split}$$

## 8.1.2. Weibull Distribution

Using the Kalbfleisch and Prentice (2002) notation:

$$\begin{split} f(t) &= \lambda p (\lambda t)^{p-1} e^{-(\lambda t)^p} \\ F(t) &= 1 - e^{-(\lambda t)^p} \\ S(t) &= e^{-(\lambda t)^p} \\ h(t) &= \lambda p (\lambda t)^{p-1} \\ H(t) &= (\lambda t)^p \\ \log \left\{ H(t) \right\} &= p \log \left\{ \lambda t \right\} = p \log \left\{ \lambda \right\} + p \log \left\{ t \right\} \\ \mathrm{E}(T) &= \lambda^{-1} \cdot \Gamma \left( 1 + \frac{1}{p} \right) \end{split}$$

## Note

Recall from calculus:

- $\Gamma(t) \stackrel{\text{def}}{=} \int_{u=0}^{\infty} u^{t-1} e^{-u} du$
- $\Gamma(t) = (t-1)!$  for integers  $t \in \mathbb{Z}$
- It is implemented by the gamma() function in R.



Here are some Weibull density functions, with  $\lambda = 1$  and p varying:

```
library(ggplot2)
lambda = 1
ggplot() +
  geom_function(
   aes(col = "0.25"),
  fun = \((x)\) dweibull(x, shape = 0.25, scale = 1/lambda)) +
```

```
geom_function(
  aes(col = "0.5"),
  fun = \(x) dweibull(x, shape = 0.5, scale = 1/lambda)) +
geom_function(
  aes(col = "1"),
  fun = \(x) dweibull(x, shape = 1, scale = 1/lambda)) +
geom_function(
  aes(col = "1.5"),
  fun = \(x) dweibull(x, shape = 1.5, scale = 1/lambda)) +
geom_function(
  aes(col = "2"),
  fun = \(x) dweibull(x, shape = 2, scale = 1/lambda)) +
geom_function(
  aes(col = "5"),
  fun = (x) dweibull(x, shape = 5, scale = 1/lambda)) +
theme_bw() +
xlim(0, 2.5) +
ylab("f(t)") +
theme(axis.title.y = element_text(angle=0)) +
theme(legend.position="bottom") +
guides(
  col =
    guide_legend(
      title = "p",
      label.theme =
        element text(
          size = 12)))
```



Figure 8.1.: Density functions for Weibull distribution

## 8.1.2.1. Properties of Weibull hazard functions

- When p=1, the Weibull distribution simplifies to the exponential distribution
- When p > 1, the hazard is increasing
- When p < 1, the hazard is decreasing

## In HW: prove these properties

This distribution provides more flexibility than the exponential.

Here are some Weibull hazard functions, with  $\lambda = 1$  and p varying:

```
library(ggplot2)
library(eha)
lambda = 1
ggplot() +
  geom_function(
    aes(col = "0.25"),
    fun = (x) hweibull(x, shape = 0.25, scale = 1/lambda)) +
  geom_function(
    aes(col = "0.5"),
    fun = \(x) hweibull(x, shape = 0.5, scale = 1/lambda)) +
  geom_function(
    aes(col = "1"),
    fun = (x) hweibull(x, shape = 1, scale = 1/lambda)) +
  geom_function(
    aes(col = "1.5"),
    fun = \(x) hweibull(x, shape = 1.5, scale = 1/lambda)) +
  geom_function(
    aes(col = "2"),
    fun = (x) hweibull(x, shape = 2, scale = 1/lambda)) +
  theme_bw() +
  xlim(0, 2.5) +
  ylab("h(t)") +
  theme(axis.title.y = element_text(angle=0)) +
  theme(legend.position="bottom") +
  guides(
    col =
      guide_legend(
        title = "p",
        label.theme =
          element_text(
            size = 12)))
```



Figure 8.2.: Hazard functions for Weibull distribution

```
library(ggplot2)
lambda = 1

ggplot() +
  geom_function(
    aes(col = "0.25"),
    fun = \(x) pweibull(lower = FALSE, x, shape = 0.25, scale = 1/lambda)) +
  geom_function(
    aes(col = "0.5"),
    fun = \(x) pweibull(lower = FALSE, x, shape = 0.5, scale = 1/lambda)) +
  geom_function(
    aes(col = "1"),
    fun = \(x) pweibull(lower = FALSE, x, shape = 1, scale = 1/lambda)) +
    geom_function(
```

```
aes(col = "1.5"),
  fun = \(x) pweibull(lower = FALSE, x, shape = 1.5, scale = 1/lambda)) +
geom_function(
  aes(col = "2"),
  fun = \(x) pweibull(lower = FALSE, x, shape = 2, scale = 1/lambda)) +
theme_bw() +
xlim(0, 2.5) +
ylab("S(t)") +
theme(axis.title.y = element_text(angle=0)) +
theme(legend.position="bottom") +
guides(
  col =
    guide_legend(
     title = "p",
      label.theme =
        element_text(
          size = 12)))
```



Figure 8.3.: Survival functions for Weibull distribution

## 8.1.3. Exponential Regression

For each subject i, define a linear predictor:

$$\begin{split} \eta(x) &= \beta_0 + (\beta_1 x_1 + \dots + \beta_p x_p) \\ h(t|x) &= \exp \left\{ \eta(x) \right\} \\ h_0 &\stackrel{\text{def}}{=} h(t|0) \\ &= \exp \left\{ \eta(0) \right\} \\ &= \exp \left\{ \beta_0 + (\beta_1 \cdot 0 + \dots + \beta_p \cdot 0) \right\} \\ &= \exp \left\{ \beta_0 + 0 \right\} \\ &= \exp \left\{ \beta_0 \right\} \end{split}$$

We let the linear predictor have a constant term, and when there are no additional predictors the hazard is  $\lambda = \exp{\{\beta_0\}}$ . This has a log link as in a generalized linear model. Since the hazard does not depend on t, the hazards are (trivially) proportional.

### 8.1.4. Accelerated Failure Time

Previously, we assumed the hazards were proportional; that is, the covariates multiplied the baseline hazard function:

$$\begin{split} h(T=t|X=x) &\stackrel{\text{def}}{=} p(T=t|X=x, T \geq t) \\ &= h(t|X=0) \cdot \exp\left\{\eta(x)\right\} \\ &= h(t|X=0) \cdot \theta(x) \\ &= h_0(t) \cdot \theta(x) \end{split}$$

and correspondingly,

$$\begin{split} H(t|x) &= \theta(x) H_0(t) \\ S(t|x) &= \exp\left\{-H(t|x)\right\} \\ &= \exp\left\{-\theta(x) \cdot H_0(t)\right\} \\ &= \left(\exp\left\{-H_0(t)\right\}\right)^{\theta(x)} \\ &= \left(S_0(t)\right)^{\theta(x)} \end{split}$$

An alternative modeling assumption would be

$$S(t|X=x) = S_0(t \cdot \theta(x))$$

where  $\theta(x)=\exp\{\eta(x)\}$ ,  $\eta(x)=\beta_1x_1+\cdots+\beta_px_p$ , and  $S_0(t)=P(T\geq t|X=0)$  is the base survival function.

Then

$$\begin{split} E(T|X=x) &= \int_{t=0}^{\infty} S(t|x) dt \\ &= \int_{t=0}^{\infty} S_0(t \cdot \theta(x)) dt \\ &= \int_{u=0}^{\infty} S_0(u) du \cdot \theta(x)^{-1} \\ &= \theta(x)^{-1} \cdot \int_{u=0}^{\infty} S_0(u) du \\ &= \theta(x)^{-1} \cdot \mathrm{E}(T|X=0) \end{split}$$

So the mean of T given X=x is the baseline mean divided by  $\theta(x)=\exp{\{\eta(x)\}}.$ 

This modeling strategy is called an accelerated failure time model, because covariates cause uniform acceleration (or slowing) of failure times.

Additionally:

$$H(t|x) = H_0(\theta(x) \cdot t)$$
  
$$h(t|x) = \theta(x) \cdot h_0(\theta(x) \cdot t)$$

If the base distribution is exponential with parameter  $\lambda$  then

$$\begin{split} S(t|x) &= \exp\left\{-\lambda \cdot t\theta(x)\right\} \\ &= \left[\exp\left\{-\lambda t\right\}\right]^{\theta(x)} \end{split}$$

which is an exponential model with base hazard multiplied by  $\theta(x)$ , which is also the proportional hazards model.

In terms of the log survival time  $Y = \log \{T\}$  the model can be written as

$$Y = \alpha - \eta + W$$
$$\alpha = -\log \{\lambda\}$$

where W has the extreme value distribution. The estimated parameter  $\lambda$  is the intercept and the other coefficients are those of  $\eta$ , which will be the opposite sign of those for coxph.

For a Weibull distribution, the hazard function and the survival function are

$$h(t) = \lambda p(\lambda t)^{p-1}$$
  
$$S(t) = e^{-(\lambda t)^p}$$

We can construct a proportional hazards model by using a linear predictor  $\eta_i$  without constant term and letting  $\theta_i = e^{\eta_i}$  we have

$$h(t) = \lambda p(\lambda t)^{p-1} \theta_i$$

A distribution with  $h(t)=\lambda p(\lambda t)^{p-1}\theta_i$  is a Weibull distribution with parameters  $\lambda^*=\lambda\theta_i^{1/p}$  and p so the survival function is

$$S^*(t) = e^{-(\lambda^* t)^p}$$

$$= e^{-(\lambda \theta^{1/p} t)^p}$$

$$= S(t\theta^{1/p})$$

so this is also an accelerated failure time model.

In terms of the log survival time  $Y = \log\{T\}$  the model can be written as

$$Y = \alpha - \sigma \eta + \sigma W$$
$$\alpha = -\log \{\lambda\}$$
$$\sigma = 1/p$$

where W has the extreme value distribution. The estimated parameter  $\lambda$  is the intercept and the other coefficients are those of  $\eta$ , which will be the opposite sign of those for coxph.

These AFT models are log-linear, meaning that the linear predictor has a log link. The exponential and the Weibull are the only log-linear models that are simultaneously proportional hazards models. Other parametric distributions can be used for survival regression either as a proportional hazards model or as an accelerated failure time model.

#### 8.1.5. Dataset: Leukemia treatments

Remission survival times on 42 leukemia patients, half on new treatment, half on standard treatment.

This is the same data as the drug6mp data from KMsurv, but with two other variables and without the pairing.

```
library(haven)
library(survival)
anderson =
  paste0(
    "http://web1.sph.emory.edu/dkleinb/allDatasets",
    "/surv2datasets/anderson.dta") |>
  read_dta() |>
  mutate(
    status = status |>
    case_match(
    1 ~ "relapse",
```

```
0 ~ "censored"
),
sex = sex |>
    case_match(
    0 ~ "female",
    1 ~ "male"
),

rx = rx |>
    case_match(
    0 ~ "new",
    1 ~ "standard"
),

surv = Surv(time = survt, event = (status == "relapse"))
)
print(anderson)
```

## 8.1.5.1. Cox semi-parametric model

```
anderson.cox0 = coxph(
  formula = surv ~ rx,
  data = anderson)
summary(anderson.cox0)

Call:
coxph(formula = surv ~ rx, data = anderson)
  n= 42, number of events= 30
```

```
coef exp(coef) se(coef)
                                     z Pr(>|z|)
                4.817 0.412 3.81 0.00014 ***
rxstandard 1.572
Signif. codes: 0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
          exp(coef) exp(-coef) lower .95 upper .95
rxstandard
               4.82
                        0.208
                                  2.15
Concordance= 0.69 (se = 0.041)
Likelihood ratio test= 16.4 on 1 df,
                                     p=5e-05
                   = 14.5 on 1 df,
                                     p=1e-04
Score (logrank) test = 17.2 on 1 df, p=3e-05
```

## 8.1.5.2. Weibull parametric model

```
anderson.weib <- survreg(
  formula = surv ~ rx,
  data = anderson,
  dist = "weibull")
summary(anderson.weib)</pre>
```

```
Call:
```

Scale= 0.732

```
Weibull distribution

Loglik(model) = -106.6 Loglik(intercept only) = -116.4

Chisq = 19.65 on 1 degrees of freedom, p= 9.3e-06

Number of Newton-Raphson Iterations: 5

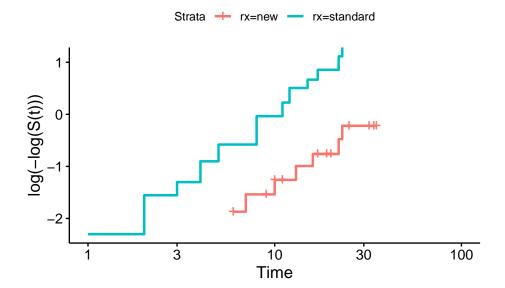
n= 42
```

### 8.1.5.3. Exponential parametric model

```
anderson.exp <- survreg(</pre>
 formula = surv ~ rx,
 data = anderson,
 dist = "exp")
summary(anderson.exp)
Call:
survreg(formula = surv ~ rx, data = anderson, dist = "exp")
             Value Std. Error
                                  z
(Intercept) 3.686 0.333 11.06 < 2e-16
rxstandard -1.527
                     0.398 -3.83 0.00013
Scale fixed at 1
Exponential distribution
Loglik(model) = -108.5
                      Loglik(intercept only) = -116.8
   Chisq= 16.49 on 1 degrees of freedom, p= 4.9e-05
Number of Newton-Raphson Iterations: 4
n = 42
```

## 8.1.5.4. Diagnostic - complementary log-log survival plot

```
library(survminer)
survfit(
  formula = surv ~ rx,
  data = anderson) |>
  ggsurvplot(fun = "cloglog")
```



If the cloglog plot is linear, then a Weibull model may be ok.

## 8.2. Combining left-truncation and interval-censoring

From [https://stat.ethz.ch/pipermail/r-help/2015-August/431733.html]:

coxph does left truncation but not left (or interval) censoring survreg does interval censoring but not left truncation (or time dependent covariates).

• Terry Therneau, August 31, 2015

- Anderson, Edgar. 1935. "The Irises of the Gaspe Peninsula." Bulletin of American Iris Society 59: 2–5.
- Bache, Stefan Milton, and Hadley Wickham. 2022. Magrittr: A Forward-Pipe Operator for r. https://CRAN.R-project.org/package=magrittr.
- Canchola, Alison J, Susan L Stewart, Leslie Bernstein, Dee W West, Ronald K Ross, Dennis Deapen, Richard Pinder, et al. 2003. "Cox Regression Using Different Time-Scales." Western Users of SAS Software. https://www.lexjansen.com/wuss/2003/DataAnalysis/i-cox\_time\_scales.pdf.
- Casella, George, and Roger Berger. 2002. Statistical Inference. 2nd ed. Cengage Learning. https://www.cengage.com/c/statistical-inference-2e-casella-berger/9780534243128/.
- Chang, Winston. 2024. R Graphics Cookbook: Practical Recipes for Visualizing Data. O'Reilly Media. https://r-graphics.org/.
- Chatterjee, Samprit, and Ali S Hadi. 2015. Regression Analysis by Example. John Wiley & Sons. https://www.wiley.com/en-us/Regression+Analysis+by+Example%2C+4th+Edition-p-9780470055458.
- Dalgaard, Peter. 2008. "Introductory Statistics with r." https://link.springer.com/book/10.1007/978-0-387-79054-1.
- Dobson, Annette J, and Adrian G Barnett. 2018. An Introduction to Generalized Linear Models. 4th ed. CRC press. https://doi.org/10.1201/9781315182780.
- Dunn, Peter K, Gordon K Smyth, et al. 2018. Generalized Linear Models with Examples in r. Vol. 53. Springer. https://link.springer.com/book/10.1007/978-1-4419-0118-7.

- Efron, Bradley, and David V Hinkley. 1978. "Assessing the Accuracy of the Maximum Likelihood Estimator: Observed Versus Expected Fisher Information." *Biometrika* 65 (3): 457–83.
- Fay, Colin, Sébastien Rochette, Vincent Guyader, and Cervan Girard. 2021. Engineering Production-Grade Shiny Apps. Chapman; Hall/CRC. https://engineering-shiny.org/.
- Fieller, Nick. 2016. Basics of Matrix Algebra for Statistics with r. Chapman; Hall/CRC. https://doi.org/10.1201/9781315370200.
- Grambsch, Patricia M, and Terry M Therneau. 1994. "Proportional Hazards Tests and Diagnostics Based on Weighted Residuals." *Biometrika* 81 (3): 515–26. https://doi.org/10.1093/biomet/81.3.515.
- Klein, John P, Melvin L Moeschberger, et al. 2003. Survival Analysis: Techniques for Censored and Truncated Data. Vol. 1230. Springer. https://link.springer.com/book/10.1007/b97377.
- Kleinbaum, David G, and Mitchel Klein. 2010. Logistic Regression. 3rd ed. Springer. https://link.springer.com/book/10.1007/978-1-4419-1742-3.
- ——. 2012. Survival Analysis a Self-Learning Text. 3rd ed. Springer. https://link.springer.com/book/10.1007/978-1-4419-6646-9.
- Kleinbaum, David G, Lawrence L Kupper, Azhar Nizam, K Muller, and ES Rosenberg. 2014. Applied Regression Analysis and Other Multivariable Methods. 5th ed. Cengage Learning. https://www.cengage.com/c/applied-regression-analysis-and-other-multivariable-methods-5e-kleinbaum/9781285051086/.
- Kutner, Michael H, Christopher J Nachtsheim, John Neter, and William Li. 2005. Applied Linear Statistical Models. McGraw-Hill.
- Lawrance, Rachael, Evgeny Degtyarev, Philip Griffiths, Peter Trask, Helen Lau, Denise D'Alessio, Ingolf Griebsch, Gudrun Wallenstein, Kim Cocks, and Kaspar Rufibach. 2020. "What Is an Estimand, and How Does It Relate to Quantifying the Effect of Treatment on Patient-Reported Quality of Life Outcomes in Clinical Trials?" Journal of Patient-Reported Outcomes 4 (1): 1–8. https://link.springer.com/article/10.1186/s41687-020-00218-5.
- McLachlan, Geoffrey J, and Thriyambakam Krishnan. 2007. The EM

- Algorithm and Extensions. 2nd ed. John Wiley & Sons. https://doi.org/10.1002/9780470191613.
- Moore, Dirk F. 2016. Applied Survival Analysis Using r. Vol. 473. Springer.
- Pebesma, Edzer, and Roger Bivand. 2023. Spatial Data Science: With Applications in R. Boca Raton: Chapman; Hall/CRC. https://doi.org/10.1201/9780429459016.
- Pohl, Moritz, Lukas Baumann, Rouven Behnisch, Marietta Kirchner, Johannes Krisam, and Anja Sander. 2021. "Estimands—A Basic Element for Clinical Trials." *Deutsches Ärzteblatt International* 118 (51-52): 883–88. https://doi.org/10.3238/arztebl.m2021.0373.
- Seber, George AF, and Alan J Lee. 2012. Linear Regression Analysis. 2nd ed. John Wiley & Sons. https://www.wiley.com/en-us/Linear+Regression+Analysis%2C+2nd+Edition-p-9781118274422.
- Van Buuren, Stef. 2018. Flexible Imputation of Missing Data. CRC press. https://stefvanbuuren.name/fimd/.
- Venables, Bill. 2023. codingMatrices: Alternative Factor Coding Matrices for Linear Model Formulae. https://CRAN.R-project.org/package=codingMatrices.
- Vittinghoff, Eric, David V Glidden, Stephen C Shiboski, and Charles E McCulloch. 2012. Regression Methods in Biostatistics: Linear, Logistic, Survival, and Repeated Measures Models. 2nd ed. Springer. https://doi.org/10.1007/978-1-4614-1353-0.
- Wickham, Hadley. 2019. Advanced r. Chapman; Hall/CRC. https://adv-r.hadley.nz/index.html.
- ——. 2021. Mastering Shiny. "O'Reilly Media, Inc.". https://mastering-shiny.org/.
- Wickham, Hadley, Mara Averick, Jennifer Bryan, Winston Chang, Lucy D'Agostino McGowan, Romain François, Garrett Grolemund, et al. 2019. "Welcome to the tidyverse." *Journal of Open Source Software* 4 (43): 1686. https://doi.org/10.21105/joss.01686.
- Wickham, Hadley, and Jennifer Bryan. 2023. *R Packages*. "O'Reilly Media, Inc.". https://r-pkgs.org/.
- Wickham, Hadley, Mine Çetinkaya-Rundel, and Garrett Grolemund. 2023.

 $\label{eq:reconstruction} R\ for\ Data\ Science.\ "\ O'Reilly\ Media,\ Inc.".\ https://r4ds.hadley.nz/.$ 

# A. Probability

## A.1. Random variables

## A.1.1. Types of random variables

**Definition A.1** (binary variable). A **binary variable** is a random variable which has only two possible values in its range.

Examples of binary outcomes include:

- exposure (exposed vs unexposed)
- disease (diseased vs healthy)
- recovery (recovered vs unrecovered)
- relapse (relapse vs remission)
- return to hospital (returned vs not)
- vital status (dead vs alive)

## A.2. Key probability distributions

**Definition A.2** (Bernoulli distribution). The **Bernoulli distribution** family for a random variable X is defined as:

$$\begin{split} \Pr(X = x) &= \mathbb{1}_{x \in \{1\}} \pi^x (1 - \pi)^{1 - x} \\ &= \left\{ \begin{matrix} \pi, x = 1 \\ 1 - \pi, x = 0 \end{matrix} \right. \end{split}$$

## A.3. Characteristics of probability distributions

**Definition A.3** (Density function). The density function f(t) for a random variable T at value t can be defined as the derivative of the cumulative probability function  $P(T \le t)$ ; that is:

$$f(t) \stackrel{\text{def}}{=} \frac{d}{dt} \Pr(T \le t)$$

**Definition A.4** (Hazard function). The hazard function for a random variable T at value t is the conditional density of T at t, given  $T \ge t$ ; that is:

$$h(t) \stackrel{\text{def}}{=} p(T = t | T \ge t)$$

If T represents the time at which an event occurs, then h(t) is the probability that the event occurs at time t, given that it has not occurred prior to time t.

**Definition A.5** (Expectation, expected value ). The expectation or expected value of a random variable X, denoted  $\mathbb{E}[X]$ ,  $\mu(X)$ , or  $\mu_X$ , is its mean:

$$\mathbb{E}\left[X\right] = \int_{x \in \mathcal{R}X} x \cdot p(X = x) dx$$

(c.f. https://en.wikipedia.org/wiki/Expected\_value)

**Definition A.6** (Variance). The variance of a random variable X is the expectation of the squared difference between X and  $\mathbb{E}[X]$ ; that is:

$$\operatorname{Var}\left(X\right)\stackrel{\operatorname{def}}{=}\mathbb{E}\left[\left(X-\mathbb{E}\left[X\right]\right)^{2}\right]$$

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Theorem A.1 (Alternative expression for variance).

$$Var(X) = \mathbb{E}\left[X^2\right] - \left(\mathbb{E}\left[X\right]\right)^2$$

*Proof.* By linearity of expectation, we have:

$$\begin{split} \operatorname{Var}\left(X\right) &\stackrel{\text{def}}{=} \mathbb{E}\left[(X - \mathbb{E}\left[X\right])^2\right] \\ &= \mathbb{E}\left[X^2 - 2X\mathbb{E}\left[X\right] + \left(\mathbb{E}\left[X\right]\right)^2\right] \\ &= \mathbb{E}\left[X^2\right] - \mathbb{E}\left[2X\mathbb{E}\left[X\right]\right] + \mathbb{E}\left[\left(\mathbb{E}\left[X\right]\right)^2\right] \\ &= \mathbb{E}\left[X^2\right] - 2\mathbb{E}\left[X\right]\mathbb{E}\left[X\right] + \left(\mathbb{E}\left[X\right]\right)^2 \\ &= \mathbb{E}\left[X^2\right] - \left(\mathbb{E}\left[X\right]\right)^2 \end{split}$$

**Definition A.7** (Precision). The **precision** of a random variable X, often denoted  $\tau(X)$ ,  $\tau_X$ , or shorthanded as  $\tau$ , is the inverse of that random variable's variance; that is:

$$\tau(X) \stackrel{\mathrm{def}}{=} \left( \mathrm{Var} \left( X \right) \right)^{-1}$$

**Definition A.8** (Standard deviation). The standard deviation of a random variable X is the square-root of the variance of X:

$$SD(X) \stackrel{\text{def}}{=} \sqrt{Var(X)}$$

**Definition A.9** (Covariance). For any two one-dimensional random variables, X, Y:

$$\operatorname{Cov}(X,Y) \stackrel{\text{def}}{=} \mathbb{E}\left[ (X - EX)(Y - EY) \right]$$

Theorem A.2.

$$Cov(X, Y) = E[XY] - E[X]E[Y]$$

*Proof.* Left to the reader.

Lemma A.1.

$$Cov(X, X) = Var(X)$$

Proof.

$$\begin{aligned} \operatorname{Cov}\left(X,X\right) &= E[XX] - E[X]E[X] \\ &= E[X^2] - (E[X])^2 \\ &= \operatorname{Var}\left(X\right) \end{aligned}$$

**Definition A.10** (Variance/covariance of a  $p \times 1$  random vector). For a  $p \times 1$  dimensional random vector X,

$$\begin{aligned} \operatorname{Var}(X) &\stackrel{\text{def}}{=} \operatorname{Cov}(X) \\ &\stackrel{\text{def}}{=} E[(X - E[X])^{\top} \left(X - E[X]\right)] \end{aligned}$$

**Theorem A.3** (Alternate expression for variance of a random vector).

$$Var(X) = E[X^{\top}X] - E[X]^{\top}E[X]$$

Proof.

$$\begin{aligned} \operatorname{Var}\left(X\right) &= E[\left(X^{\top} - E[X]^{\top}\right) \left(X - E[X]\right)] \\ &= E[X^{\top}X - E[X]^{\top}X - X^{\top}E[X] + E[X]^{\top}E[X]] \\ &= E[X^{\top}X] - E[X]^{\top}E[X] - E[X]^{\top}E[X] + E[X]^{\top}E[X] \\ &= E[X^{\top}X] - 2E[X]^{\top}E[X] + E[X]^{\top}E[X] \\ &= E[X^{\top}X] - E[X]^{\top}E[X] \end{aligned}$$

## A. Probability

**Definition A.11** (Statistical independence). A set of random variables  $X_1, \ldots, X_n$  are **statistically independent** if their joint probability is equal to the product of their marginal probabilities:

$$\Pr(X_1=x_1,\dots,X_n=x_n)=\prod_{i=1}^n\Pr(X_i=x_i)$$

**Definition A.12** (homoskedastic). A random variable Y is **homoskedastic** (with respect to covariates X) if the variance of Y does not vary with X:

$$Var(Y|X=x) = \sigma^2, \forall x$$

Otherwise it is **heteroskedastic**.

## **B.** Estimation

## **B.1. Probabilistic models**

**Definition B.1** (Scientific models). **Scientific models** are attempts to describe *physical conditions or changes* that occur in the world and universe around us.

**Example B.1** (Scientific models in epidemiology). Epidemiologists typically study *biological conditions and changes*, such as the spread of infectious diseases through populations, or the effects of environmental factors on individuals.

## B.1.1. Statistical analysis of scientific models

When we perform statistical analyses, we use data to help us choose between models - specifically, to determine which models best explain that data.

However, physical processes do not produce data on their own. Data is only produced when scientists implement an *observation process* (i.e., a *scientific study*), which is distinct from the underlying *physical process*. In

#### B. Estimation

some cases, the observation process and the physical process interact with each other. This phenomenon is called the "observer effect".

In order to learn about the physical processes we are ultimately interested in, we often need to make special considerations for the observation process that produced the data which we are analyzing. In particular, if some of the planned observations in the study design were not completed, we will likely need to account for the incompleteness of the resulting data set in our analysis. If we are not sure why some observations are incomplete, we may need to model the observation process in addition to the physical process we were originally interested in. For example, if some participants in a study dropped out part-way through the study, we may need investigate why those participants dropped out, as opposed to other participants who completed the study.

These kinds of *missing data* issues are outside of the scope of this course; see Van Buuren (2018) for more details.

## B.2. Estimands, estimates, and estimators

### **B.2.1.** Estimands

**Definition B.2** (Estimand). An **estimand** is an unknown quantity whose value we want to know (Pohl et al. 2021; Lawrance et al. 2020).

**Example B.2** (Mean height of students). If we are trying to determine the mean height of students at our school, then the *population mean* is our **estimand**.

In statistical contexts, most estimands are parameters of probabilistic models, or functions of model parameters.

<sup>&</sup>lt;sup>1</sup>https://en.wikipedia.org/wiki/Observer effect

#### i Notation for estimands

Model paramaters and other estimands are often symbolized using lower-case Greek letters:  $\alpha, \beta, \gamma, \delta$ , etc.

#### **B.2.2.** Estimates

**Definition B.3** (Estimate/estimated value). In statistics, an **estimate** or **estimated value** is an informed guess of an estimand's value, based on observed data.

**Example B.3** (Mean height of students). Suppose we measure the heights of 50 random students from our school, and the sample mean was 175cm. We might use 175cm as an *estimate* of the population mean.

#### **B.2.3.** Estimators

**Definition B.4** (Estimator). An **estimator** is a function  $\hat{\theta}(x_1,...x_n)$  that transforms data  $x_1,...x_n$  into an estimate.

#### i Estimators are random variables

When estimators are applied to random variables, the estimators are also random variables.

#### Notation for estimators

Estimators are often symbolized by placing a  $\hat{\theta}$  ("hat") symbol on top of the corresponding estimand; for example,  $\hat{\theta}$ . Usually, their dependence on the data is implicit:

$$\hat{\theta} \stackrel{\text{def}}{=} \hat{\theta}(x_1,...x_n)$$

**Example B.4** (Mean height of students). If we want to estimate the mean height of students at our university, which we will represent as  $\mu$ , we might measure the heights of n=50 randomly sampled students as random variables  $X_1, ..., X_n$ . Then we could use the function

$$\hat{\mu}(X_1,...,X_n) = \frac{1}{n} \sum_{i=1}^n X_i \stackrel{\text{def}}{=} \bar{X}$$

as an estimator to produce an estimate  $\hat{\mu} = \bar{x}$  of  $\mu$ .

Another estimator would be just the height of the first student sampled:

$$\hat{\mu}^{(2)}(X_1,...,X_n) = X_1$$

A third possible estimator would be the mean of all sampled students' heights, except for the two most extreme; that is, if we re-order the observations  $X_{(1)} = \min_{i \in 1:n} X_i$ ,  $X_{(2)} = \min_{i \in \{1:n\} - \arg X_{(1)}} X_i$ , ...,  $X_{(n)} = \max_{i \in 1:n} X_i$ , then we could define the estimator:

$$\hat{\mu}^{(3)}(X_1,...,X_n) = \frac{1}{n} \sum_{i=2}^{n-1} X_{(i)}$$

Which of these estimators is best? It depends on how we evaluate them (see Section B.3 below).

#### B.2.4. Contrasting estimands, estimates, and estimators

It's helpful to keep in mind the mathematical type of each estimation concept:

- estimands are numbers (or vector of numbers)
- estimates are also numbers (or vectors)
- estimators are functions of random variables, so they are also random variables

#### **B.3.** Accuracy of estimators

#### B.3.1. Accuracy

To determine which estimator is best, we need to define *best*. "Accuracy" is usually most important; easy computation is usually secondary.

**Definition B.5** (Accuracy). The **accuracy** of an estimator for a given estimand does not have a consensus formal definition, but all of the usual candidates are related to the distributions of the *errors* made by the resulting estimates.

#### B.3.2. Error

**Definition B.6** (Error). The **error** of an estimate  $\hat{\theta}$  of a true value  $\theta$ , often denoted  $\epsilon(\hat{\theta})$ , or more completely  $\epsilon(\hat{\theta}, \theta)$ , is the difference between the estimate and its estimand  $\theta$ ; that is:

$$\epsilon(\hat{\theta}) \stackrel{\text{def}}{=} \hat{\theta} - \theta$$

Some frequently-used measures of accuracy include:

#### B.3.3. Mean squared error

**Definition B.7** (Mean squared error). The **mean squared error** of an estimator  $\hat{\theta}$ , denoted MSE  $(\hat{\theta})$ , is the expectation of the square of the error<sup>2</sup>:

$$MSE\left(\hat{\theta}\right) \stackrel{\text{def}}{=} \mathbb{E}\left[\left(\epsilon(\hat{\theta})\right)^{2}\right]$$

#### B.3.4. Mean absolute error

**Definition B.8** (Mean absolute error). The **mean absolute error** of an estimator is the expectation of the absolute value of the error:

$$\operatorname{MAE}\left(\hat{\theta}\right) \stackrel{\operatorname{def}}{=} \mathbb{E}\left[\left|\epsilon(\hat{\theta})\right|\right]$$

#### **B.3.5.** Bias

**Definition B.9** (Bias). The **bias** of an estimator  $\hat{\theta}$  for an estimand  $\theta$  is the expected value of the error:

$$\operatorname{Bias}\left(\hat{\theta}\right) \stackrel{\operatorname{def}}{=} \mathbb{E}\left[\epsilon(\hat{\theta})\right] \tag{B.1}$$

Theorem B.1 (Bias equals Expectation minus Truth).

$$Bias\left( \widehat{\theta}\right) =\mathbb{E}\left[ \widehat{\theta}\right] -\theta$$

 $<sup>^{2}\</sup>mathrm{I}$  might sometimes switch the order of  $x,\,\theta;$  this is unintentional and not meaningful.

Proof.

$$\begin{aligned} \operatorname{Bias}\left(\hat{\theta}\right) & \stackrel{\operatorname{def}}{=} \mathbb{E}\left[\epsilon(\hat{\theta})\right] \\ &= \mathbb{E}\left[\hat{\theta} - \theta\right] \\ &= \mathbb{E}\left[\hat{\theta}\right] - \mathbb{E}\left[\theta\right] \\ &= \mathbb{E}\left[\hat{\theta}\right] - \theta \end{aligned}$$

The third equality is by the linearity of expectation.

**Theorem B.2** (Mean Squared Error equals Bias Squared plus Variance). For any one-dimensional estimator  $\hat{\theta}$ :

$$MSE(\hat{\theta}) = \left(Bias(\hat{\theta})\right)^2 + Var(\hat{\theta})$$
 (B.2)

*Proof.* Let's start by expanding each term of the right-hand side:

$$\begin{split} \left( \mathrm{Bias} \left( \hat{\theta} \right) \right)^2 &= \left( \mathbb{E} \left[ \hat{\theta} \right] - \theta \right)^2 \\ &= \left( \mathbb{E} \left[ \hat{\theta} \right] \right)^2 - 2 \mathbb{E} \left[ \hat{\theta} \right] \theta + \theta^2 \end{split}$$
 
$$\mathrm{Var} \left( \hat{\theta} \right) &= \mathbb{E} \left[ \hat{\theta}^2 \right] - \left( \mathbb{E} \left[ \hat{\theta} \right] \right)^2 \end{split}$$

Now, add them together and simplify:

$$\begin{split} \left( \mathrm{Bias} \left( \hat{\theta} \right) \right)^2 + \mathrm{Var} \left( \hat{\theta} \right) &= \left( \mathbb{E} \left[ \hat{\theta} \right] \right)^2 - 2 \mathbb{E} \left[ \hat{\theta} \right] \theta + \theta^2 + \mathbb{E} \left[ \hat{\theta}^2 \right] - \left( \mathbb{E} \left[ \hat{\theta} \right] \right)^2 \\ &= \mathbb{E} \left[ \hat{\theta}^2 \right] - 2 \mathbb{E} \left[ \hat{\theta} \right] \theta + \theta^2 \end{split}$$

Now let's expand the left-hand side to reach the same expression:

$$\begin{split} \text{MSE} \left( \hat{\theta} \right) &= \mathbb{E} \left[ (\epsilon(\hat{\theta}))^2 \right] \\ &= \mathbb{E} \left[ (\hat{\theta} - \theta)^2 \right] \\ &= \mathbb{E} \left[ \hat{\theta}^2 - 2\hat{\theta}\theta - \theta^2 \right] \\ &= \mathbb{E} \left[ \hat{\theta}^2 \right] - \mathbb{E} \left[ 2\hat{\theta}\theta \right] + \mathbb{E} \left[ \theta^2 \right] \\ &= \mathbb{E} \left[ \hat{\theta}^2 \right] - 2\mathbb{E} \left[ \hat{\theta} \right] \theta + \theta^2 \end{split}$$

$$MSE(\hat{\theta}) = (Bias(\hat{\theta}))^{2} + Var(\hat{\theta})$$

#### **B.3.5.1.** Unbiased estimators

**Definition B.10** (unbiased estimator). An estimator  $\hat{\theta}$  is **unbiased** if  $\operatorname{Bias}\left(\hat{\theta}\right)=0.$ 

**Theorem B.3** (properties of unbiased estimators). If  $\hat{\theta}$  is unbiased, then:

$$\mathbb{E}\left[\hat{\theta}\right] = \theta \tag{B.3}$$

$$MSE(\hat{\theta}) = Var(\hat{\theta})$$
 (B.4)

*Proof.* If  $\hat{\theta}$  is unbiased, then:

Equation B.3:

$$\begin{aligned} \operatorname{Bias}\left(\widehat{\theta}\right) &= 0 \\ \mathbb{E}\left[\widehat{\theta}\right] - \theta &= 0 \\ \mathbb{E}\left[\widehat{\theta}\right] &= \theta \end{aligned}$$

Equation B.4:

$$\begin{split} \operatorname{MSE}\left(\hat{\theta}\right) &\stackrel{\text{def}}{=} \mathbb{E}\left[\left(\epsilon(\hat{\theta})\right)^{2}\right] \\ &= \mathbb{E}\left[\left(\hat{\theta} - \theta\right)^{2}\right] \\ &= \mathbb{E}\left[\left(\hat{\theta} - \mathbb{E}\left[\hat{\theta}\right]\right)^{2}\right] \\ &\stackrel{\text{def}}{=} \operatorname{Var}\left(\hat{\theta}\right) \end{split}$$

(Alternative proof of Equation B.4) We could have started from Theorem B.2 instead:

$$\begin{aligned} \text{MSE} \left( \hat{\theta} \right) &= \left( \text{Bias} \left( \hat{\theta} \right) \right)^2 + \text{Var} \left( \hat{\theta} \right) \\ &= \left( 0 \right)^2 + \text{Var} \left( \hat{\theta} \right) \\ &= 0 + \text{Var} \left( \hat{\theta} \right) \\ &= \text{Var} \left( \hat{\theta} \right) \end{aligned}$$

#### **B.3.6.** Standard error

**Definition B.11** (Standard error). The **standard error** of an estimator  $\hat{\theta}$  is just the **standard deviation** of  $\hat{\theta}$ ; that is:

$$\operatorname{SE}\left(\hat{\theta}\right) \stackrel{\mathrm{def}}{=} \operatorname{SD}\left(\hat{\theta}\right)$$

"Standard error" is a confusing concept in a few ways. First of all, it isn't even defined as a characteristic of the error,  $\epsilon(\hat{\theta})$ ! Moreover, it is just a synonym for standard deviation, so it seems like a redundant concept. However, standard errors help us construct p-values and confidence intervals, so they come up a lot - often enough to give them their own name.

We can relate standard error to actual error, by rearranging the result from Theorem B.2:

$$\begin{aligned} \operatorname{Var}\left(\hat{\theta}\right) &= \operatorname{Var}\left(\hat{\theta} - \theta\right) \\ &= \operatorname{Var}\left(\epsilon(\hat{\theta})\right) \end{aligned}$$

So the variance of the estimator is equal to the variance of the error, and the standard error is equal to the standard deviation of the error:

$$SE(\hat{\theta}) = SD(\epsilon(\hat{\theta}))$$

**Corollary B.1** (Standard error squared equals MSE minus squared bias). standard error is what is left over of MSE after bias is removed:

$$\left(SE\left(\hat{\theta}\right)\right)^{2} = MSE\left(\hat{\theta}\right) - \left(Bias\left(\hat{\theta}\right)\right)^{2}$$

Proof.

$$\begin{aligned} \operatorname{MSE}\left(\hat{\theta}\right) &= \left(\operatorname{Bias}\left(\hat{\theta}\right)\right)^{2} + \operatorname{Var}\left(\hat{\theta}\right) \\ & : \operatorname{Var}\left(\hat{\theta}\right) &= \operatorname{MSE}\left(\hat{\theta}\right) - \left(\operatorname{Bias}\left(\hat{\theta}\right)\right)^{2} \\ & : \left(\operatorname{SE}\left(\hat{\theta}\right)\right)^{2} &= \operatorname{MSE}\left(\hat{\theta}\right) - \left(\operatorname{Bias}\left(\hat{\theta}\right)\right)^{2} \end{aligned}$$

Corollary B.2 (For unbiased estimators, SE = RMSE). If  $\mathbb{E}\left[\epsilon\left(\hat{\theta}\right)\right]=0$ , then:

$$SE\left(\hat{\theta}\right) = \sqrt{MSE\left(\hat{\theta}\right)}$$

(this result is equivalent to Equation B.4)

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These notes are derived primarily from Dobson and Barnett (2018) (mostly chapters 1-5).

Some material was also taken from McLachlan and Krishnan (2007) and Casella and Berger (2002).

#### C.1. Overview of maximum likelihood estimation

#### C.1.1. The likelihood function

**Definition C.1** (Likelihood). Let  $\tilde{x}$  be a dataset with corresponding random variable  $\tilde{X}$ . Let  $p_{\Theta}(\tilde{X})$  be a probability model for the distribution of  $\tilde{X}$  with parameter vector  $\Theta$ .

Then the **likelihood** of parameter value  $\theta$ , for model  $p_{\Theta}(X)$  and data  $\tilde{X} = \tilde{x}$ , is the *joint probability* of  $\tilde{x}$  given  $\Theta = \theta$ :

$$\begin{split} \mathcal{L}(\theta) & \stackrel{\text{def}}{=} p_{\theta}(\tilde{X} = \tilde{x}) \\ &= p_{\theta}(X_1 = x_1, ..., X_n = x_n) \end{split}$$

#### Notation for the likelihood function

The likelihood function can be written as:

- $\mathcal{L}(\theta)$
- $\mathcal{L}(\tilde{x};\theta)$
- $\mathcal{L}(\theta; \tilde{x})$
- L<sub>π</sub>(θ)
- $\mathcal{L}_{o}(\tilde{x})$
- $\mathcal{L}(\tilde{x}|\theta)$

All of these notations mean the same thing.

The likelihood is a function that takes  $\theta$  (and implicitly,  $\tilde{X}$ ) as inputs and outputs a single number, the joint probability of  $\tilde{x}$  for model  $p_{\Theta}(\tilde{X}=\tilde{x})$  with  $\Theta=\theta$ .

**Theorem C.1** (Likelihood of an independent sample). For mutually independent data  $X_1, ..., X_n$ :

$$\mathcal{L}(\tilde{x}|\theta) = \prod_{i=1}^{n} p(X_i = x_i|\theta)$$
 (C.1)

Proof.

$$\begin{split} \mathcal{L}(\tilde{x}|\theta) &\stackrel{\text{def}}{=} \mathbf{p}(X_1 = x_1, ..., X_n = x_n|\theta) \\ &= \prod_{i=1}^n \mathbf{p}(X_i = x_i|\theta) \end{split}$$

The second equality is by the definition of statistical independence.  $\Box$ 

#### C.1.2. The maximum likelihood estimate

**Definition C.2** (Maximum likelihood estimate). The **maximum likelihood estimate** of a parameter vector  $\Theta$ , denoted  $\hat{\theta}_{ML}$ , is the value of  $\Theta$  that maximizes the likelihood:

$$\hat{\theta}_{\mathrm{ML}} \stackrel{\mathrm{def}}{=} \arg \max_{\Theta} \mathcal{L}(\Theta) \tag{C.2}$$

#### C.1.3. Finding the maximum of a function

Recall from calculus: the maxima of a continuous function f(x) over a range of input values  $\Re x$  can be found either:

- at the edges of the range of input values, OR:
- where the function is flat (i.e. where the gradient function f'(x) = 0) AND the second derivative is negative definite (f''(x) < 0).

#### C.1.4. Directly maximizing the likelihood function for iid data

To find the maximizer(s) of the likelihood function, we need to solve  $\mathcal{L}'(\theta) = 0$  for  $\theta$ . However, even for mutually independent data, we quickly run into a problem:

$$\mathcal{L}'(\theta) = \frac{d}{d\theta} \mathcal{L}(\theta)$$

$$= \frac{d}{d\theta} \prod_{i=1}^{n} p(X_i = x_i | \theta)$$
(C.3)

The derivative of the likelihood of independent data is the derivative of a product. We will have to perform a massive application of the product rule to evaluate this derivative.

#### C.1.5. The log-likelihood function

It is typically easier to work with the log of the likelihood function:

**Definition C.3** (Log-likelihood). The **log-likelihood** of parameter value  $\theta$ , for model  $p_{\Theta}(\tilde{X})$  and data  $\tilde{X} = \tilde{x}$ , is the natural logarithm of the likelihood<sup>1</sup>:

$$\ell(\theta) \stackrel{\text{def}}{=} \log \left\{ \mathcal{L}(\theta) \right\}$$

**Theorem C.2.** The likelihood and log-likelihood have the same maximizer:

$$\arg\max_{\theta} \mathcal{L}(\theta) = \arg\max_{\theta} \ell(\theta)$$

*Proof.* Left to the reader.

**Theorem C.3** (Log-likelihood of an iid sample). For iid data  $X_1,...,X_n$  with shared distribution p(X=x):

$$\ell(x|\theta) = \sum_{i=1}^{n} \log \left\{ p(X = x_i|\theta) \right\} \tag{C.4} \label{eq:condition}$$

 $<sup>^{1}</sup> https://en.wikipedia.org/wiki/Does\_exactly\_what\_it\_says\_on\_the\_tin$ 

Proof.

$$\begin{split} \ell(x|\theta) &\stackrel{\text{def}}{=} \log \left\{ \mathcal{L}(\tilde{x}|\theta) \right\} \\ &= \log \left\{ \prod_{i=1}^n \mathrm{p}(X_i = x_i|\theta) \right\} \\ &= \sum_{i=1}^n \log \left\{ p(X = x_i|\theta) \right\} \end{split}$$

For iid data, we will have a much easier time taking the derivative of the log-likelihood:

**Theorem C.4** (Derivative of the log-likelihood function for iid data). For  $iid\ data$ :

$$\ell'(\theta) = \sum_{i=1}^{n} \frac{d}{d\theta} \log \left\{ p(X = x_i | \theta) \right\}$$
 (C.5)

Proof.

$$\begin{split} \ell'(\theta) &= \frac{d}{d\theta} \ell(\theta) \\ &= \frac{d}{d\theta} \sum_{i=1}^n \log \left\{ \mathbf{p}(X = x_i | \theta) \right\} \\ &= \sum_{i=1}^n \frac{d}{d\theta} \log \left\{ \mathbf{p}(X = x_i | \theta) \right\} \end{split}$$

#### C.1.6. The score function

The first derivative of the log-likelihood,  $\ell'(\theta)$ , is important enough to have its own name: the *score function*.

**Definition C.4** (Score function). The **score function** of a statistical model  $p(\tilde{X} = \tilde{x})$  is the gradient (i.e., first derivative) of the log-likelihood of that model:

$$\ell'(\theta) \stackrel{\text{def}}{=} \frac{d}{d\theta} \ell(\theta)$$

We often skip writing the arguments x and/or  $\theta$ ), so  $\ell' \stackrel{\text{def}}{=} \ell'(\tilde{x}; \theta) \stackrel{\text{def}}{=} \ell'(\theta)$ . Some statisticians use U or S instead of  $\ell'$ . I prefer  $\ell'$ . Why use up extra letters?

### C.1.7. Asymptotic distribution of the maximum likelihood estimate

We learned how to quantify our uncertainty about these maximum likelihood estimates; with sufficient sample size,  $\hat{\theta}_{\rm ML}$  has the approximate distribution:

$$\hat{\theta}_{ML} \dot{\sim} N(\theta, \mathcal{I}(\theta)^{-1})$$

Recall:

- $\mathcal{I}(\theta) \stackrel{\text{def}}{=} \mathbb{E}\left[I(\tilde{X}; \theta)\right]$
- $I(\tilde{X}, \theta) \stackrel{\text{def}}{=} -\ell''(\tilde{X}; \theta)$

<sup>&</sup>lt;sup>2</sup>I might sometimes switch the order of x,  $\theta$ ; this is unintentional and not meaningful.

We can estimate  $\mathcal{I}(\theta)$  using either  $\mathcal{I}(\hat{\theta}_{\mathrm{ML}})$  or  $I(\tilde{x}; \hat{\theta}_{\mathrm{ML}})$ .

So we can estimate the standard error of  $\hat{\theta}_k$  as:

$$\widehat{\mathrm{SE}}\left(\widehat{\boldsymbol{\theta}}_{k}\right) = \sqrt{\left[\left(\widehat{\mathcal{I}}\left(\widehat{\boldsymbol{\theta}}_{\mathrm{ML}}\right)\right)^{-1}\right]_{kk}}$$

#### C.1.8. The (Fisher) (expected) information matrix

The variance of  $\ell'(x,\theta)$ ,  $Cov\{\ell'(x,\theta)\}$ , is also very important; we call it the "expected information matrix", "Fisher information matrix", or just "information matrix", and we represent it using the symbol  $\Im$  (\frakturI in Unicode, \mathfrak{I} in LaTeX).

$$\mathfrak{I} \stackrel{\mathrm{def}}{=} \mathfrak{I}(\theta) \stackrel{\mathrm{def}}{=} Cov\left(\ell'|\theta\right) = E[{\ell'}{\ell'}^{\top}] - E[\ell'] \ E[\ell']^{\top}$$

The elements of  $\Im$  are:

$$\left\{ \mathfrak{I}_{ij} \stackrel{\mathrm{def}}{=} Cov\left({\ell'}_i, {\ell'}_j\right) = E[{\ell'_i}{\ell'_j}] - E[{\ell'}_i] E[{\ell'}_j] \right\}$$

Here,

$$\begin{split} \mathbb{E}\left[\ell'\right] &\stackrel{\text{def}}{=} \int_{x \in \mathcal{R}x} \ell'(x,\theta) \mathbf{p}(X=x|\theta) dx \\ &= \int_{x \in \mathcal{R}X} \left(\frac{d}{d\theta} \log \left\{\mathbf{p}(X=x|\theta)\right\}\right) \mathbf{p}(X=x|\theta) dx \\ &= \int_{x \in \mathcal{R}X} \frac{\frac{d}{d\theta} \mathbf{p}(X=x|\theta)}{\mathbf{p}(X=x|\theta)} \mathbf{p}(X=x|\theta) dx \\ &= \int_{x \in \mathcal{R}X} \frac{d}{d\theta} \mathbf{p}(X=x|\theta) dx \end{split}$$

And similarly

$$\mathbb{E}\left[\ell'\ell'^{\top}\right] \stackrel{\mathrm{def}}{=} \int_{x \in R(x)} \ell'(x,\theta) \ell'(x,\theta)^{\top} \ \mathbf{p}\left(X = x | \theta\right) \ dx$$

Note that  $\mathbb{E}\left[\ell'\right]$  and  $\mathbb{E}\left[\ell'{\ell'}^{\top}\right]$  are functions of  $\theta$  but not of x; the expectation operator removed x.

Also note that for most of the distributions you are familiar with (including Gaussian, binomial, Poisson, exponential):

$$\mathbb{E}\left[\ell'\right] = 0$$

So

$$\mathcal{I}\left(\boldsymbol{\theta}\right) = \mathbb{E}\left[\boldsymbol{\ell}'\boldsymbol{\ell'}^{\top}\right]$$

Moreover, for those distributions (called the "exponential family"), we have:

$$\Im = -\mathbb{E}\left[\ell''\right] = \mathbb{E}\left[-\ell''\right]$$

(see Dobson and Barnett (2018), §3.17), where

$$\ell'' \stackrel{\text{def}}{=} \frac{d}{d\theta} \ell'(x,\theta)^{\top} = \frac{d}{d\theta} \frac{d}{d\theta^{\top}} \ell(x,\theta)$$

is the  $p \times p$  matrix whose elements are:

$$\ell_{ij}'' \stackrel{\mathrm{def}}{=} \frac{d}{d\theta_i} \frac{d}{d\theta_j} \log \left\{ p\left(X = x \mid \theta\right) \right\}$$

 $\ell''$  could be called the "Hessian" of the log-likelihood function.

Sometimes, we use  $I(\theta;x) \stackrel{\text{def}}{=} -\ell''$  (note the standard-font "I" here).  $I(\theta;x)$  is the observed information, precision, or concentration matrix (Negative Hessian).

#### Key point

The asymptotics of MLEs gives us  $\hat{\theta}_{ML} \sim N\left(\theta, \Im^{-1}(\theta)\right)$ , approximately, for large sample sizes.

We can estimate  $\mathcal{I}^{-1}(\theta)$  by working out  $\mathbb{E}\left[-\ell''\right]$  or  $\mathbb{E}\left[\ell'\ell'^{\top}\right]$  and plugging in  $\hat{\theta}_{\mathrm{ML}}$ , but sometimes we instead use  $I(\hat{\theta}_{\mathrm{ML}}, \tilde{x})$  for convenience; there are some cases where it's provably better according to some criteria (Efron and Hinkley (1978)).

#### C.1.9. Gradient ascent

Note that later, when we are trying to find MLEs for likelihoods that we can't easily differentiate, we will "hill-climb" using the Newton-Raphson algorithm:

$$\begin{split} \hat{\theta} &\leftarrow \hat{\theta} + [I\left(\hat{\theta}, y\right)]^{-1} \ell'\left(y, \hat{\theta}\right) \\ &= \hat{\theta} - [\ell''\left(y, \hat{\theta}\right)]^{-1} \ell'\left(y, \hat{\theta}\right) \end{split}$$

Here, for computational simplicity, we will sometimes use  $\mathfrak{I}^{-1}(\theta)$  in place of  $I\left(\hat{\theta},y\right)$ ; doing so is called "Fisher scoring" or the "method of scoring". Note that this is the opposite of the substitution that we are making for estimating the variance of the MLE; this time we should technically use the observed information but we use the expected information instead.

There's also an "empirical information matrix" (see McLachlan and Krishnan 2007).

$$I_e(\theta,y) = \sum_{i=1}^n \ell_i' \; {\ell_i'}^\top - \frac{1}{n} {\ell'} {\ell'}^\top$$

where  $\ell_i$  is the log-likelihood of the ith observation. Note that  $\ell' = \sum_{i=1}^{n} \ell'_i$ .

 $\frac{1}{n}I_e(\theta,y)$  is the sample equivalent of

$$\mathfrak{I} \stackrel{\text{def}}{=} \mathfrak{I}(\theta) \stackrel{\text{def}}{=} Cov\left(\ell'|\theta\right) = E[\ell'{\ell'}^\top] - E[\ell'] \ E[\ell']^\top$$

$$\left\{ \Im_{jk} \stackrel{\mathrm{def}}{=} Cov\left({\ell'}_j, {\ell'}_k\right) = E[{\ell'_j}{\ell'_k}] - E[{\ell'}_j]E[{\ell'}_k] \right\}$$

 $I_e(\theta,y)$  is sometimes computationally easier to compute for Newton-Raphson-type maximization algorithms.

#### C.1.9.1. Confidence intervals for MLEs

An asymptotic approximation of a 95% confidence interval for  $\theta_k$  is

$$\widehat{\boldsymbol{\theta}}_{\mathrm{ML}} \pm \boldsymbol{z}_{0.975} \times \widehat{\mathrm{SE}} \left( \widehat{\boldsymbol{\theta}}_{k} \right)$$

where  $z_{\beta}$  the  $\beta$  quantile of the standard Gaussian distribution.

#### C.1.9.2. p-values and hypothesis tests for MLEs

(to add)

#### C.1.9.3. Likelihood ratio tests for MLEs

log(likelihood ratio) tests (c.f. Dobson and Barnett 2018, sec. 5.7):

$$-2\ell_0 \sim \chi^2(p-q)$$

See also https://online.stat.psu.edu/stat504/book/export/html/657

#### C.1.9.4. Prediction intervals for MLEs

$$\overline{X} \in [\hat{\mu} \pm z_{1-\alpha/2} \frac{\sigma}{m}]$$

Where m is the sample size of the new data to be predicted (typically 1, except for binary outcomes, where it needs to be bigger for prediction intervals to make sense)

# C.2. Example: Maximum likelihood for Tropical Cyclones in Australia

(Adapted from Dobson and Barnett (2018) §1.6.5)

#### C.2.1. Data

The cyclones dataset in the dobson package (Table C.1) records the number of tropical cyclones in Northeastern Australia during 13 November-to-April cyclone seasons (more details in Dobson and Barnett (2018) §1.6.5 and help(cyclones, package = "dobson")). Figure C.1 graphs the number of cyclones (y-axis) by season (x-axis). Let's use  $Y_i$  to represent these counts, where i is an indexing variable for the seasons and  $Y_i$  is the number of cyclones in season i.

#### C.2.2. Exploratory analysis

Suppose we want to learn about how many cyclones to expect per season.

```
library(dobson)
library(dplyr)
data(cyclones)
library(pander)
pander(cyclones |> relocate(season, .before = everything()))
```

Table C.1.: Number of tropical cyclones during a season from November to April in Northeastern Australia

season	years	number
1	1956/7	6
2	1957/8	5
3	1958/9	4
4	1959/60	6
5	1960/1	6
6	1961/2	3
7	1962/3	12
8	1963/4	7
9	1964/5	4
10	1965/6	2
11	1966/7	6
12	1967/8	7
13	1968/9	4

```
library(ggplot2)
library(dplyr)
cyclones |>
  mutate(years = years |> factor(level = years)) |>
```

```
ggplot(
  aes(x = years,
      y = number,
      group = 1)) +

geom_point() +

geom_line() +

xlab("Season") +

ylab("Number of cyclones") +

theme_bw() +

expand_limits(y = 0) +

theme(axis.text.x = element_text(vjust = .5, angle = 45))
```

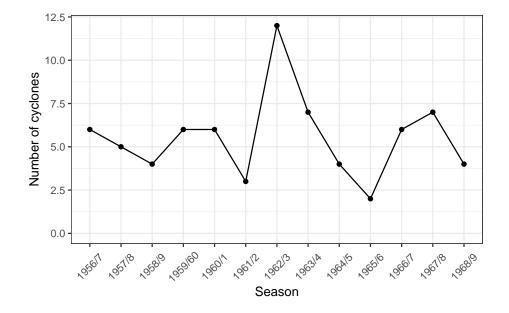


Figure C.1.: Number of tropical cyclones per season in northeastern Australia, 1956-1969

There's no obvious correlation between adjacent seasons, so let's assume that each season is independent of the others.

Let's also assume that they are identically distributed; let's denote this distribution as P(Y=y) (note that there's no index i in this expression, since we are assuming the  $Y_i$ s are identically distributed). We can visualize the distribution using a bar plot (Figure C.2). Table C.2 provides summary statistics.

```
cyclones |>
  ggplot() +
  geom_histogram(aes(x = number)) +
  expand_limits(x = 0) +
  theme_bw() +
  xlab("Number of cyclones") +
  ylab("Count (number of seasons)")
```

Table C.2.: Summary statistics for cyclones data

	Overall	
	(N=13)	
number		
Mean (SD)	5.54(2.47)	
Median [Min, Max]	6.00 [2.00, 12.0]	

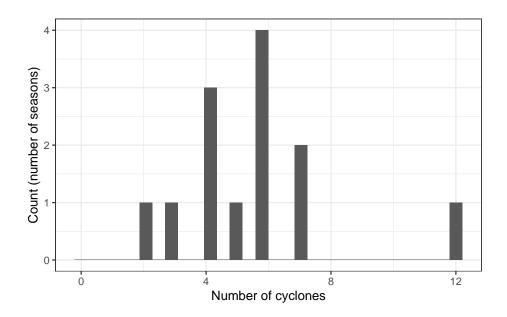


Figure C.2.: Bar plot of cyclones per season

cyclones |> table1::table1(x = ~ number)

#### C.2.3. Model

We want to estimate P(Y = y); that is, P(Y = y) is our estimand.

We could estimate P(Y=y) for each value of y in  $0:\infty$  separately ("nonparametrically") using the fraction of our data with  $Y_i=y$ , but then we would be estimating an infinitely large set of parameters, and we would have low precision. We will probably do better with a parametric model.

Exercise C.1. What parametric probability distribution family might we use to model this empirical distribution?

Solution. Let's use the Poisson. The Poisson distribution is appropriate for this data , because the data are counts that could theoretically take any integer value (discrete) in the range  $0:\infty$ . Visually, the plot of our data closely resembles a Poisson or binomial distribution. Since cyclones do not have an "upper limit" on the number of events we could potentially observe in one season, the Poisson distribution is more appropriate than the binomial.

**Exercise C.2.** Write down the Poisson distribution's probability mass function.

Solution.

$$P(Y=y) = \frac{\lambda^y e^{-\lambda}}{y!}$$

## C.2.4. Estimating the model parameters using maximum likelihood

Now, we can estimate the parameter  $\lambda$  for this distribution using maximum likelihood estimation.

What is the likelihood?

**Exercise C.3.** Write down the likelihood (probability mass function or probability density function) of a single observation x, according to your model.

Solution.

$$\begin{split} \mathcal{L}(\lambda;x) &= p(X = x | \Lambda = \lambda) \\ &= \frac{\lambda^x e^{-\lambda}}{x!} \end{split}$$

Exercise C.4. Write down the vector of parameters in your model.

Solution. There is only one parameter,  $\lambda$ :

$$\theta = (\lambda)$$

**Exercise C.5.** Write down the population mean and variance of a single observation from your chosen probability model, as a function of the parameters (extra credit - derive them).

Solution.

- Population mean:  $E[X] = \lambda$
- Population variance:  $Var(X) = \lambda$

Exercise C.6. Write down the likelihood of the full dataset.

Solution.

$$\begin{split} \mathcal{L}(\lambda; \tilde{x}) &= P(\tilde{X} = \tilde{x}) \\ &= P(X_1 = x_1, X_2 = x_2, ..., X_{13} = x_{13}) \\ &= \prod_{i=1}^{13} P(X_i = x_i) \\ &= \prod_{i=1}^{13} \frac{\lambda^{x_i} e^{-\lambda}}{x_i!} \end{split}$$

**Exercise C.7.** Graph the likelihood as a function of  $\lambda$ .

Solution.

```
lik = function(lambda, y = cyclones$number, n = length(y))
{
   lambda^sum(y) * exp(-n*lambda) / prod(factorial(y))
}

library(ggplot2)
ggplot() +
   geom_function(fun = lik, n = 1001) +
   xlim(min(cyclones$number), max(cyclones$number)) +
   theme_bw() +
   ylab("likelihood") +
   xlab('lambda')
```

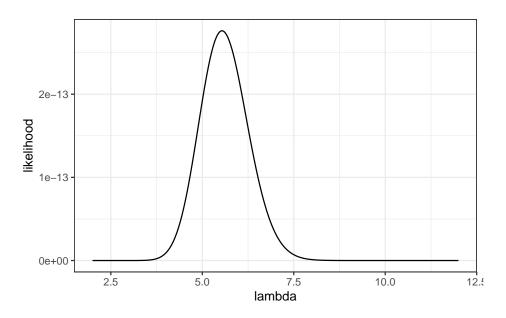


Figure C.3.: Likelihood of Dobson cyclone data

**Exercise C.8.** Write down the log-likelihood of the full dataset.

Solution.

$$\begin{split} \ell(\lambda;\tilde{x}) &= \log \left\{ \mathcal{L}(\lambda;\tilde{x}) \right\} \\ &= \log \left\{ \prod_{i=1}^n \frac{\lambda^{x_i} \mathrm{e}^{-\lambda}}{x_i!} \right\} \\ &= \sum_{i=1}^n \log \left\{ \frac{\lambda^{x_i} \mathrm{e}^{-\lambda}}{x_i!} \right\} \\ &= \sum_{i=1}^n \log \left\{ \lambda^{x_i} \right\} + \log \left\{ \mathrm{e}^{-\lambda} \right\} - \log \left\{ x_i! \right\} \\ &= \sum_{i=1}^n x_i \log \left\{ \lambda \right\} - \lambda - \log \left\{ x_i! \right\} \\ &= \sum_{i=1}^n x_i \log \left\{ \lambda \right\} - \sum_{i=1}^n \lambda - \sum_{i=1}^n \log \left\{ x_i! \right\} \\ &= \sum_{i=1}^n x_i \log \left\{ \lambda \right\} - n\lambda - \sum_{i=1}^n \log \left\{ x_i! \right\} \end{split}$$

**Exercise C.9.** Graph the log-likelihood as a function of  $\lambda$ .

Solution.

```
loglik = function(lambda, y = cyclones$number, n = length(y))
{
   sum(y) * log(lambda) - n*lambda - sum(log(factorial(y)))
}

ll_plot = ggplot() +
   geom_function(fun = loglik, n = 1001) +
   xlim(min(cyclones$number), max(cyclones$number)) +
   theme_bw() +
   ylab("log-likelihood") +
```

```
xlab('lambda')
ll_plot
```

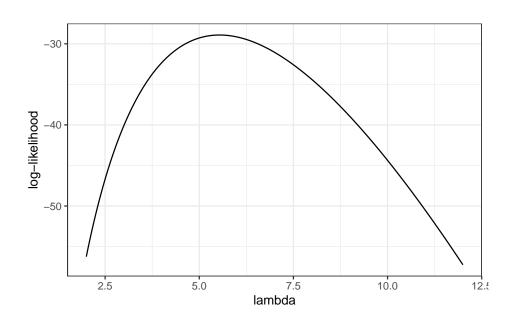


Figure C.4.: log-likelihood of Dobson cyclone data

Exercise C.10. Derive the score function for the dataset.

Solution. The score function is the first derivative(s) of the log-likelihood:

$$\begin{split} \ell'(\lambda; \tilde{x}) &= \frac{\partial}{\partial \lambda} \sum_{i=1}^n x_i \log \left\{ \lambda \right\} - n\lambda - \sum_{i=1}^n \log \left\{ x_i ! \right\} \\ &= \frac{\partial}{\partial \lambda} \sum_{i=1}^n x_i \log \left\{ \lambda \right\} - \frac{\partial}{\partial \lambda} n\lambda - \frac{\partial}{\partial \lambda} \sum_{i=1}^n \log \left\{ x_i ! \right\} \\ &= \sum_{i=1}^n x_i \frac{\partial}{\partial \lambda} \log \left\{ \lambda \right\} - n \frac{\partial}{\partial \lambda} \lambda - \sum_{i=1}^n \frac{\partial}{\partial \lambda} \log \left\{ x_i ! \right\} \\ &= \sum_{i=1}^n x_i \frac{1}{\lambda} - n - 0 \\ &= \frac{1}{\lambda} \sum_{i=1}^n x_i - n \end{split}$$

Exercise C.11. Graph the score function.

Solution.

```
score = function(lambda, y = cyclones$number, n = length(y))
{
    sum(y)/lambda - n
}

ggplot() +
    geom_function(fun = score, n = 1001) +
    xlim(min(cyclones$number), max(cyclones$number)) +
    theme_bw() +
    ylab("l'(lambda)") +
    xlab('lambda') +
    geom_hline(yintercept = 0, col = 'red')
```

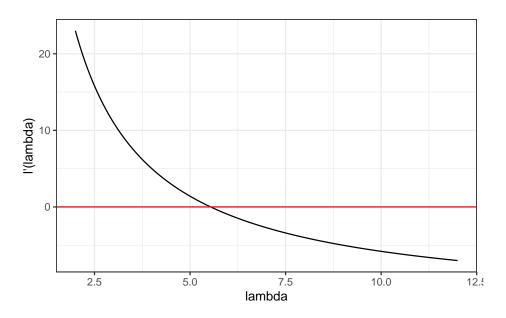


Figure C.5.: score function of Dobson cyclone data

#### Exercise C.12. Derive the Hessian matrix.

Solution. The Hessian function for an iid sample is the 2nd derivative(s) of the log-likelihood:

$$\begin{split} \ell''(\lambda;\tilde{x}) &= \frac{\partial}{\partial \lambda} \left( \frac{1}{\lambda} \sum_{i=1}^n x_i - n \right) \\ &= \frac{\partial}{\partial \lambda} \frac{1}{\lambda} \sum_{i=1}^n x_i - \frac{\partial}{\partial \lambda} n \\ &= -\frac{1}{\lambda^2} \sum_{i=1}^n x_i \\ &= -\frac{1}{\lambda^2} n \bar{x} \end{split}$$

#### Exercise C.13. Graph the Hessian.

Solution.

```
hessian = function(lambda, y = cyclones$number, n = length(y))
{
    -sum(y)/lambda^2
}

ggplot() +
    geom_function(fun = hessian, n = 1001) +
    xlim(min(cyclones$number), max(cyclones$number)) +
    theme_bw() +
    ylab("l''(lambda)") +
    xlab('lambda') +
    geom_hline(yintercept = 0, col = 'red')
```

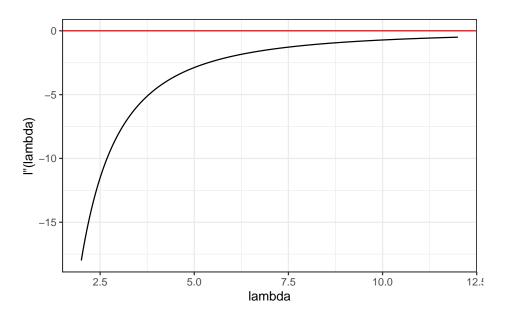


Figure C.6.: Hessian function of Dobson cyclone data

Exercise C.14. Write the score equation (estimating equation).

Solution.

$$\ell'(\lambda;\tilde{x})=0$$

**Exercise C.15.** Solve the estimating equation for  $\lambda$ :

Solution.

$$0 = \frac{1}{\lambda} \sum_{i=1}^{n} x_i - n$$

$$n = \frac{1}{\lambda} \sum_{i=1}^{n} x_i$$

$$n\lambda = \sum_{i=1}^{n} x_i$$

$$\lambda = \frac{1}{n} \sum_{i=1}^{n} x_i$$

$$= \bar{x}$$

Let's call this solution of the estimating equation  $\tilde{\lambda}$  for now:

$$\tilde{\lambda} \stackrel{\text{def}}{=} \bar{x}$$

**Exercise C.16.** Confirm that the Hessian  $\ell''(\lambda; \tilde{x})$  is negative when evaluated at  $\tilde{\lambda}$ .

Solution.

$$\ell''(\tilde{\lambda}; \tilde{x}) = -\frac{1}{\tilde{\lambda}^2} n \bar{x}$$

$$= -\frac{1}{\bar{x}^2} n \bar{x}$$

$$= -\frac{n}{\bar{x}}$$

**Exercise C.17.** Find the MLE of  $\lambda$ .

Solution. Since  $\ell''(\tilde{\lambda}; \tilde{x}) < 0$ ,  $\tilde{\lambda}$  is at least a local maximizer of the likelihood function  $\mathcal{L}(\lambda)$ . Since there is only one solution to the estimating equation

and the Hessian is negative definite everywhere,  $\tilde{\lambda}$  must also be the global maximizer of  $\mathcal{L}(\lambda; \tilde{x})$ :

$$\hat{\lambda}_{\rm ML} = \bar{x} = 5.53846154$$

Exercise C.18. Graph the log-likelihood with the MLE superimposed.

Solution.

```
library(dplyr)

mle_data = tibble(x = mle, y = loglik(mle))

ll_plot + geom_point(data = mle_data, aes(x = x, y = y), col = 'red')
```

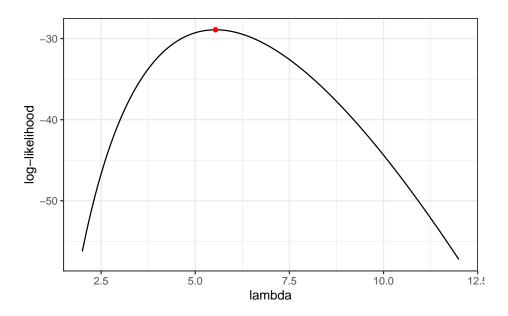


Figure C.7.: log-likelihood of Dobson cyclone data with MLE

```
obs_inf = function(lambda, y = cyclones$number, n = length(y))
{
   sum(y)/lambda^2
}
```

# C.3. Maximum likelihood inference for univariate Gaussian models

Suppose  $X_1,...,X_n \sim_{\mathrm{iid}} N(\mu,\sigma^2)$ . Let  $X=(X_1,...,X_n)^\top$  be these random variables in vector format. Let  $x_i$  and x denote the corresponding observed data. Then  $\theta=(\mu,\sigma^2)$  is the vector of true parameters, and  $\Theta=(\mathrm{M},\Sigma^2)$  is the vector of parameters as a random vector.

Then the log-likelihood is:

$$\begin{split} \ell & \propto -\frac{n}{2} \mathrm{log} \left\{ \sigma^2 \right\} - \frac{1}{2} \sum_{i=1}^n \frac{(x_i - \mu)^2}{\sigma^2} \\ & = -\frac{n}{2} \mathrm{log} \left\{ \sigma^2 \right\} - \frac{1}{2\sigma^2} \sum_{i=1}^n x_i^2 - 2x_i \mu + \mu^2 \end{split}$$

#### C.3.1. The score function

$$\ell'(x,\theta) \stackrel{\mathrm{def}}{=} \frac{d}{d\theta} \ell(x,\theta) = \left( \begin{array}{c} \frac{d}{d\mu} \ell(\theta;x) \\ \frac{d}{d\sigma^2} \ell(\theta;x) \end{array} \right) = \left( \begin{array}{c} \ell'_{\mu}(\theta;x) \\ \ell'_{\sigma^2}(\theta;x) \end{array} \right)$$

 $\ell'(x,\theta)$  is the function we set equal to 0 and solve to find the MLE:

$$\hat{\theta}_{ML} = \{\theta : \ell'(x, \theta) = 0\}$$

#### C.3.2. MLE of $\mu$

$$\begin{split} \frac{d\ell}{d\mu} &= -\frac{1}{2} \sum_{i=1}^{n} \frac{-2(x_i - \mu)}{\sigma^2} \\ &= \frac{1}{\sigma^2} \left[ \left( \sum_{i=1}^{n} x_i \right) - n\mu \right] \end{split}$$

If  $\frac{d\ell}{d\mu} = 0$ , then  $\mu = \overline{x} \stackrel{\text{def}}{=} \frac{1}{n} \sum_{i=1}^{n} x_i$ .

$$\frac{d^2\ell}{(d\mu)^2} = \frac{-n}{\sigma^2} < 0$$

So  $\hat{\mu}_{ML} = \overline{x}$ .

#### C.3.3. MLE of $\sigma^2$

#### • Reparametrizing the Gaussian distribution

When solving for  $\hat{\sigma}_{ML}$ , you can treat  $\sigma^2$  as an atomic variable (don't differentiate with respect to  $\sigma$  or things get messy). In fact, you can replace  $\sigma^2$  with  $1/\tau$  and differentiate with respect to  $\tau$  instead, and the process might be even easier.

$$\begin{split} \frac{d\ell}{d\sigma^2} &= \frac{d}{d\sigma^2} \left( -\frac{n}{2} \log \left\{ \sigma^2 \right\} - \frac{1}{2} \sum_{i=1}^n \frac{\left( x_i - \mu \right)^2}{\sigma^2} \right) \\ &= -\frac{n}{2} \left( \sigma^2 \right)^{-1} + \frac{1}{2} \left( \sigma^2 \right)^{-2} \sum_{i=1}^n \left( x_i - \mu \right)^2 \end{split}$$

If  $\frac{d\ell}{d\sigma^2} = 0$ , then:

$$\begin{split} \frac{n}{2} \left(\sigma^2\right)^{-1} &= \frac{1}{2} \left(\sigma^2\right)^{-2} \sum_{i=1}^n \left(x_i - \mu\right)^2 \\ \sigma^2 &= \frac{1}{n} \sum_{i=1}^n \left(x_i - \mu\right)^2 \end{split}$$

We plug in  $\hat{\mu}_{ML} = \overline{x}$  to maximize globally (a technique called profiling):

$$\sigma_{ML}^2 = \frac{1}{n} \sum_{i=1}^{n} \left( x_i - \overline{x} \right)^2$$

Now:

$$\begin{split} \frac{d^2\ell}{\left(d\sigma^2\right)^2} &= \frac{d}{d\sigma^2} \left\{ -\frac{n}{2} \left(\sigma^2\right)^{-1} + \frac{1}{2} \left(\sigma^2\right)^{-2} \sum_{i=1}^n \left(x_i - \mu\right)^2 \right\} \\ &= \left\{ -\frac{n}{2} \frac{d}{d\sigma^2} \left(\sigma^2\right)^{-1} + \frac{1}{2} \frac{d}{d\sigma^2} \left(\sigma^2\right)^{-2} \sum_{i=1}^n \left(x_i - \mu\right)^2 \right\} \\ &= \left\{ \frac{n}{2} \left(\sigma^2\right)^{-2} - \left(\sigma^2\right)^{-3} \sum_{i=1}^n \left(x_i - \mu\right)^2 \right\} \\ &= \left(\sigma^2\right)^{-2} \left\{ \frac{n}{2} - \left(\sigma^2\right)^{-1} \sum_{i=1}^n \left(x_i - \mu\right)^2 \right\} \end{split}$$

Evaluated at  $\mu = \overline{x}, \sigma^2 = \frac{1}{n} \sum_{i=1}^n \left(x_i - \overline{x}\right)^2$ , we have:

$$\begin{split} \frac{d^2\ell}{\left(d\sigma^2\right)^2} &= \left(\hat{\sigma}^2\right)^{-2} \left\{ \frac{n}{2} - \left(\hat{\sigma}^2\right)^{-1} \sum_{i=1}^n \left(x_i - \overline{x}\right)^2 \right\} \\ &= \left(\hat{\sigma}^2\right)^{-2} \left\{ \frac{n}{2} - \left(\hat{\sigma}^2\right)^{-1} n \hat{\sigma}^2 \right\} \\ &= \left(\hat{\sigma}^2\right)^{-2} \left\{ \frac{n}{2} - n \right\} \\ &= \left(\hat{\sigma}^2\right)^{-2} n \left\{ \frac{1}{2} - 1 \right\} \\ &= \left(\hat{\sigma}^2\right)^{-2} n \left( -\frac{1}{2} \right) < 0 \end{split}$$

Finally, we have:

$$\begin{split} \frac{d^2\ell}{d\mu\;d\sigma^2} &= \frac{d}{d\mu} \left\{ -\frac{n}{2} \left(\sigma^2\right)^{-1} + \frac{1}{2} \left(\sigma^2\right)^{-2} \sum_{i=1}^n \left(x_i - \mu\right)^2 \right\} \\ &= \frac{1}{2} \left(\sigma^2\right)^{-2} \frac{d}{d\mu} \sum_{i=1}^n \left(x_i - \mu\right)^2 \\ &= \frac{1}{2} \left(\sigma^2\right)^{-2} \sum_{i=1}^n -2(x_i - \mu) \\ &= -\left(\sigma^2\right)^{-2} \sum_{i=1}^n \left(x_i - \mu\right) \end{split}$$

Evaluated at  $\mu=\hat{\mu}=\overline{x},\sigma^2=\hat{\sigma}^2=\frac{1}{n}\sum_{i=1}^n\left(x_i-\overline{x}\right)^2$ , we have:

$$\frac{d^2\ell}{d\mu\;d\sigma^2} = -\left(\hat{\sigma}^2\right)^{-2}(n\overline{x}-n\overline{x}) = 0$$

#### C.3.4. Covariance matrix

$$I = \begin{bmatrix} \frac{n}{\sigma^2} & 0\\ 0 & (\hat{\sigma}^2)^{-2} n\left(-\frac{1}{2}\right) \end{bmatrix} = \begin{bmatrix} a & 0\\ 0 & d \end{bmatrix}$$

So:

$$I^{-1} = \frac{1}{ad} \begin{bmatrix} d & 0 \\ 0 & a \end{bmatrix} = \begin{bmatrix} \frac{1}{a} & 0 \\ 0 & \frac{1}{d} \end{bmatrix}$$
$$I^{-1} = \begin{bmatrix} \frac{\widehat{\sigma}^2}{n} & 0 \\ 0 & \frac{2(\widehat{\sigma}^2)^2}{n} \end{bmatrix}$$

See Casella and Berger (2002) p322, example 7.2.12.

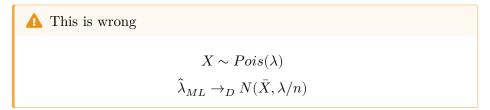
To prove it's a maximum, need:

- $\ell' = 0$
- At least one diagonal element of  $\ell''$  is negative.
- Determinant of  $\ell''$  is positive.

# D. Common Mistakes

#### D.1. Parameters versus random variables

The parameters of a probability distribution shouldn't involve the random variables being modeled:



Solution.

$$\hat{\lambda}_{ML} \to_D N(\lambda, \lambda/n)$$

Expectations are means, not sums, despite the similarity of  $\Sigma$  and E. Really, we should use  $\mu$  instead of E.

### D.2. Quarto

Make sure not to put a div ::: on the next line after a slide break ---:

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#### D. Common Mistakes

There needs to be an empty line between them:

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# **E.** Notation

Table E.1.: Notation used in this book

symbol	meaning	LaTeX
5y 111001	meaning	LateA
$\neg$	not	\neg
$\forall$	all	\forall
3	some	\exists
$\cup$	union, "or"	\cup
$\cap$	intersection, "and"	\cap
	given, conditional on	\mid,
$\sum$	sum	\sum
Π	$\operatorname{product}$	\prod
$\mu$	mean	\mu
$\mathbb{E}[X]$	expectation of $X$	\mathbb{E}[X]

# F. Statistical computing in R

There are an overwhelming number of great resources for learning R; here are some recommendations:

- Introduction to modern R: Wickham, Çetinkaya-Rundel, and Grolemund (2023)
- Advanced R programming: Wickham (2019)
- Examples of graphics: Chang (2024)
- Building R packages: Wickham and Bryan (2023)

#### F.1. Functions

- Read this ASAP: https://r4ds.hadley.nz/functions.html
- Use this as a reference: https://adv-r.hadley.nz/functions.html

## F.2. The tidyverse

The tidyverse is an opinionated collection of R packages designed for data science. All packages share an underlying design philosophy, grammar, and data structures.

• https://www.tidyverse.org/

#### F. Statistical computing in R

These packages are being actively developed by Hadley Wickham<sup>1</sup> and his colleagues at posit<sup>23</sup>.

#### Details:

- Wickham et al. (2019)
- Wickham, Cetinkaya-Rundel, and Grolemund (2023)

### F.3. Piping

See Wickham, Çetinkaya-Rundel, and Grolemund (2023)<sup>5</sup> for details.

There are currently (2024) two commonly-used pipe operators in R:

- %>%: the "magrittr pipe", from the magrittr<sup>6</sup> package (Bache and Wickham (2022); re-exported<sup>7</sup> by dplyr<sup>8</sup> and others).
- |>: the "native pipe", from base R (4.1.0)

#### F.3.1. Which pipe should I use?

Wickham, Çetinkaya-Rundel, and Grolemund (2023) recommends the native pipe<sup>9</sup>:

<sup>&</sup>lt;sup>1</sup>https://hadley.nz/

<sup>&</sup>lt;sup>2</sup>https://posit.co/

<sup>&</sup>lt;sup>3</sup>the company formerly known as RStudio<sup>4</sup>

<sup>&</sup>lt;sup>5</sup>https://r4ds.hadley.nz/data-transform.html#sec-the-pipe

<sup>&</sup>lt;sup>6</sup>https://cran.r-project.org/web/packages/magrittr/index.html

<sup>&</sup>lt;sup>7</sup>https://r-pkgs.org/dependencies-in-practice.html#re-exporting

<sup>8</sup> https://cran.r-project.org/web/packages/dplyr/index.html

<sup>9</sup>https://r4ds.hadley.nz/data-transform.html#sec-the-pipe:~:text=So%20why% 20do%20we%20recommend%20the%20base%20pipe%3F

#### F. Statistical computing in R

For simple cases, |> and %>% behave identically. So why do we recommend the base pipe? Firstly, because it's part of base R, it's always available for you to use, even when you're not using the tidyverse. Secondly, |> is quite a bit simpler than %>%: in the time between the invention of %>% in 2014 and the inclusion of |> in R 4.1.0 in 2021, we gained a better understanding of the pipe. This allowed the base implementation to jettison infrequently used and less important features.

#### F.3.2. Why doesn't ggplot2 use piping?

Here's tidyverse creator Hadley Wickham's answer (from 2018):

I think it's worth unpacking this question into a few smaller pieces:

- Should ggplot2 use the pipe? IMO, yes.
- Could ggplot2 support both the pipe and plus? No
- Would it be worth it to create a ggplot3 that uses the pipe? No.

https://forum.posit.co/t/why-cant-ggplot2-use/4372/7

#### F.4. Quarto

Quarto is a system for writing documents with embedded R code and/or results:

- Read this ASAP: https://r4ds.hadley.nz/communicate
- Then use this for reference: https://quarto.org/docs/reference/

### F.5. Packages

This book espouses our philosophy of package development: anything that can be automated, should be automated. Do as little as possible by hand. Do as much as possible with functions. The goal is to spend your time thinking about what you want your package to do rather than thinking about the minutiae of package structure.

- $\bullet \ \ https://r-pkgs.org/introduction.html \#: \sim : text = This \% 20 book \% 20 espouses, of \% 20 package \% 20 structure and the property of the package of t$
- Read this ASAP: https://r-pkgs.org/whole-game.html
- Use the rest of Wickham and Bryan (2023) as a reference

#### F.6. Git

94% of respondents to a 2022 Stack Overflow survey reported using git for version control link  $^{10}$ 

More details<sup>11</sup>

• https://happygitwithr.com/

### F.7. Spatial data science

• Pebesma and Bivand (2023)

 $<sup>^{10} \</sup>rm https://survey.stackoverflow.co/2022/\#section-version-control-version-control-systems$ 

 $<sup>^{11} \</sup>rm https://r\text{-}pkgs.org/software\text{-}development\text{-}practices.html}\#sec\text{-}sw\text{-}dev\text{-}practices\text{-}git-github}$ 

### F.8. Shiny apps

• Use this as a reference: Fay et al. (2021)

# F.9. Methods versus functions

See https://adv-r.hadley.nz/oo.html#oop-systems

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