Regression Models for Epidemiology

Ezra Morrison

Last modified: 2024-05-07: 14:03:57 (PM)

Pr	reface	1
1.	Introduction 1.1. Introduction to Epi 204	6
I.	Generalized Linear Models	19
2.	Linear (Gaussian) Models 2.1. Overview 2.2. Understanding Gaussian Linear Regression Models 2.3. Estimating Linear Models via Maximum Likelihood 2.4. Inference about Gaussian Linear Regression Models 2.5. Goodness of fit 2.6. Rescaling 2.7. Prediction 2.8. Diagnostics 2.9. Model selection 2.10. Categorical covariates with more than two levels 2.11. Ordinal covariates	44 53 59 67 69 73 108 116
3.	3.1. Introduction	126 128 130

	3.3.	Comparing probabilities
	3.4.	Properties of odds ratios
	3.5.	Introduction to logistic regression
	3.6.	Multiple logistic regression
	3.7.	Fitting logistic regression models
	3.8.	Model comparisons for logistic models 191
	3.9.	Residual-based diagnostics
	3.10.	Odds Ratios vs Probability (Risk) Ratios 214
4.	Mod	lels for Count Outcomes 217
	Ackr	nowledgements
	4.1.	Introduction
	4.2.	Inference for count regression models
	4.3.	Prediction
	4.4.	Diagnostics
	4.5.	Zero-inflation
	4.6.	Over-dispersion
II.	Tin	ne to Event Models 228
5.	Intro	oduction to Survival Analysis 230
	5.1.	Overview
	5.2.	Time-to-event outcome distributions
	5.3.	Distribution functions for time-to-event variables 233
	5.4.	Parametric Models for Time-to-Event Outcomes 250
	5.5.	Nonparametric Survival Analysis
	5.6.	Example: clinical trial for pediatric acute leukemia 254
	5.7.	The Kaplan-Meier Product Limit Estimator
	5.8.	Using the survival package in R
	5.9.	Example: Bone Marrow Transplant Data 273
	5.10	Nelson-Aalen Estimates of Cumulative Hazard and Survival 283

6.	Proportional Hazards Models	287			
	6.1. The proportional hazards model	289			
	6.2. Cox Model for the bmt data	300			
	6.3. Adjustment for Ties (optional)	310			
7.	Building Cox Proportional Hazards models				
	7.1. Building Cox Proportional Hazards models	315			
	7.2. Diagnostic graphs for proportional hazards assumption	318			
	7.3. Predictions and Residuals	327			
	7.4. Goodness of Fit using the Cox-Snell Residuals	336			
	7.5. Martingale Residuals	338			
	7.6. Checking for Outliers and Influential Observations	343			
	7.7. Stratified survival models	353			
	7.8. Time-varying covariates	365			
	7.9. Recurrent Events	381			
	7.10. Age as the time scale	387			
8.	Parametric survival models	388			
	8.1. Parametric Survival Models	390			
	8.2. Combining left-truncation and interval-censoring \dots	405			
Re	ferences	406			
Αţ	pendices	410			
Α.	Probability	410			
	A.1. Random variables	412			
	A.2. Key probability distributions	412			
	A.3. Characteristics of probability distributions				
В.	Estimation	419			
	B.1. Probabilistic models	419			
	B.2. Estimands, estimates, and estimators	420			
	B.3. Accuracy of estimators	423			

C.	Introduction to Maximum Likelihood Inference	430
	C.1. Overview of maximum likelihood estimation	432
	C.2. Example: Maximum likelihood for Tropical Cyclones in	
	Australia	443
	C.3. Maximum likelihood inference for univariate Gaussian models	5471
	C.4. Example: hormone therapy study	476
D.	Common Mistakes	494
	D.1. Parameters versus random variables	496
	D.2. Quarto	496
Ε.	Notation	498
	E.1. The percent sign	498
F.	Statistical computing in R	500
	F.1. Functions	500
	F.2. The tidyverse	501
	F.3. Piping	501
	F.4. Quarto	503
	F.5. Packages	503
	F.6. Git	503
	F.7. Spatial data science	504
	F.8. Shiny apps	504
G.	Contributing to rme	505
	G.1. Fixing typos	505
	G.2. Bigger changes	505
	G.3. Code of Conduct	507

Preface

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

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

- David Rocke¹'s materials from the 2021 edition of Epi 204²
- Vittinghoff et al. (2012)
- Dobson and Barnett (2018)

License

This book is licensed to you under Creative Commons Attribution-NonCommercial-NoDerivatives 4.0 International License³.

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

¹https://dmrocke.ucdavis.edu/

²https://dmrocke.ucdavis.edu/Class/EPI204-Spring-2021/EPI204-Spring-2021.html

³http://creativecommons.org/licenses/by-nc-nd/4.0/

⁴https://creativecommons.org/publicdomain/zero/1.0/

Configuring R

Functions from these packages will be used throughout this document:

```
library(conflicted) # check for conflicting function definitions
# library(printr) # inserts help-file output into markdown output
library(rmarkdown) # Convert R Markdown documents into a variety of formats.
library(pander) # format tables for markdown
library(ggplot2) # graphics
library(ggeasy) # help with graphics
library(ggfortify) # help with graphics
library(dplyr) # manipulate data
library(tibble) # `tibble`s extend `data.frame`s
library(magrittr) # `%>%` and other additional piping tools
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(haven) # import Stata files
```

```
library(latex2exp) # use LaTeX in R code (for figures and tables)
library(fs) # filesystem path manipulations
library(survival) # survival analysis
library(survminer) # survival analysis graphics
library(KMsurv) # datasets from Klein and Moeschberger
library(parameters) # format model output tables for
library(webshot2) # convert interactive content to static for pdf
library(forcats) # functions for categorical variables ("factors")
library(stringr) # functions for dealing with strings
library(lubridate) # functions for dealing with dates and times
```

Here are some R settings I use in this document:

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 homework¹
 - 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)
- Regression models for non-Gaussian outcomes
 - binary
 - count
 - time to event
- Statistical analysis using R

¹https://r4ds.hadley.nz/quarto

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

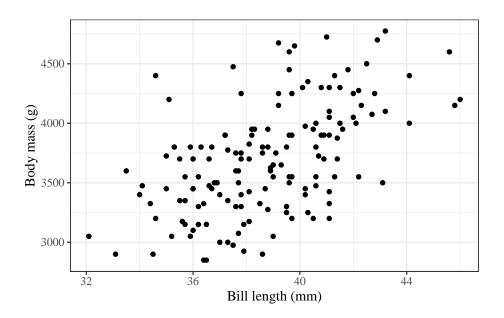


Figure 1.1.: Palmer penguins

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
```

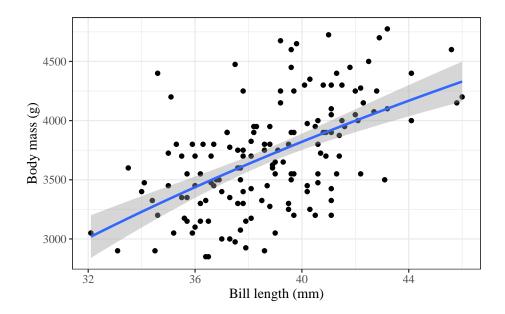


Figure 1.3.: Palmer penguins - curved regression lines

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 \sim x,
    geom = "smooth") +
  xlab("Bill length (mm)") +
 ylab("Body mass (g)")
ggpenguins |> print()
```

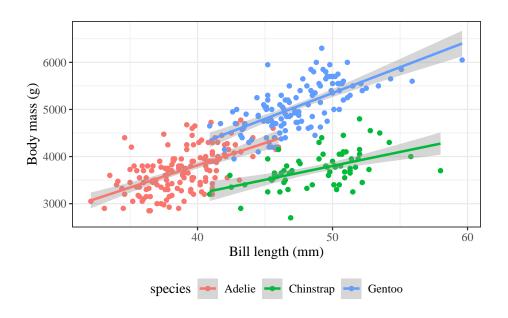


Figure 1.4.: Palmer penguins - multiple groups

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)
```

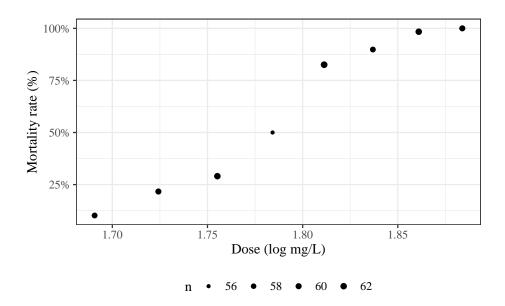


Figure 1.5.: Mortality rates of adult flour beetles after five hours' exposure to gaseous carbon disulphide (Bliss 1935)

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))
 )
lm1 =
 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)
```

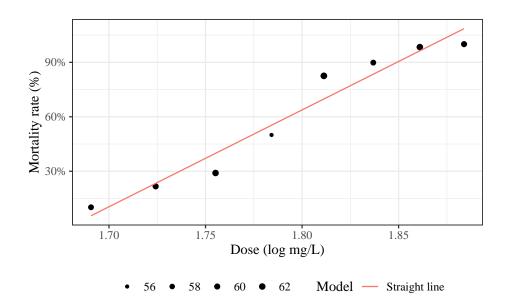


Figure 1.6.: Mortality rates of adult flour beetles after five hours' exposure to gaseous carbon disulphide (Bliss 1935)

1.2.7. **Zoom out**

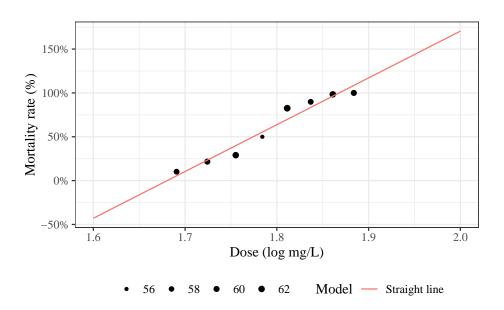


Figure 1.7.: Mortality rates of adult flour beetles after five hours' exposure to gaseous carbon disulphide (Bliss 1935)

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 1.8.: 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 1.9.: 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 tidyverse² packages (ggplot2³, dplyr⁴, 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.
- Harrell (2015) is another popular textbook. It uses ggplot2⁵ but not dplyr⁶, and covers GLMs and survival analysis. An abbreviated but continuously updated version with audio clips is available at https://hbiostat.org/rmsc/.
- Fox (2015) is another standard text.
- McCullagh and Nelder (1989) is a classic, theoretical textbook on GLMs

²https://tidyverse.org/

³https://ggplot2.tidyverse.org/

⁴https://dplyr.tidyverse.org/

⁵https://ggplot2.tidyverse.org/

⁶https://dplyr.tidyverse.org/

- Dalgaard (2008) covers GLMs and survival analysis at an applied level, using base R
- Vittinghoff et al. (2012) covers GLMs, survival analysis, and causal inference, using Stata
- Faraway (2016) has GLMs but not survival analysis
- 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.
- Nahhas (n.d.) is currently in-development

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

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; $\eta = X\beta = g(\mu)$

			•	_ (, ,
			Link	Inverse Link
Name	Domain	Range	Function	Function
identity	$(-\infty,\infty)$	$(-\infty,\infty)$	$\eta = \mu$	$\mu = \eta$
log	$(0,\infty)$	$(-\infty, \infty)$	$\eta = \log \{\mu\}$	$\mu = \exp\left\{\eta\right\}$
inverse	$(0, \infty)$	$(0,\infty)$	$\eta = 1/\mu$	$\mu = 1/\eta$
logit	(0, 1)	$(-\infty,\infty)$	$\eta =$	$\mu =$
			$\log \left\{ \mu/(1-\mu) \right\}$	μ) \Rightarrow xp $\{\eta\}/(1+$
				$\exp\left\{\eta ight\}$
probit	(0, 1)	$(-\infty,\infty)$	$\eta =$	$\mu = \Phi(\eta)$
			$\Phi^{-1}(\mu)$	
cloglog	(0, 1)	$(-\infty,\infty)$	$\eta =$	$\mu =$
			$\log \{-\log \{1$	$-1\hspace{-0.2cm}\mu\hspace{-0.2cm}+\hspace{-0.2cm}3\hspace{-0.2cm}\exp\left\{-\exp\left\{\eta\right\}\right.$
1/mu^2	$(0, \infty)$	$(0,\infty)$	$\eta = 1/\mu^2$	$\mu = 1/\sqrt{\eta}$
sqrt	$(0, \infty)$	$(0,\infty)$	$\eta = \sqrt{\mu}$	$\mu = \eta^2$
			•	

2. Linear (Gaussian) Models

Configuring R

Functions from these packages will be used throughout this document:

```
library(conflicted) # check for conflicting function definitions
# library(printr) # inserts help-file output into markdown output
library(rmarkdown) # Convert R Markdown documents into a variety of formats.
library(pander) # format tables for markdown
library(ggplot2) # graphics
library(ggeasy) # help with graphics
library(ggfortify) # help with graphics
library(dplyr) # manipulate data
library(tibble) # `tibble`s extend `data.frame`s
library(magrittr) # `%>%` and other additional piping tools
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(haven) # import Stata files
```

2. Linear (Gaussian) Models

```
library(latex2exp) # use LaTeX in R code (for figures and tables)
library(fs) # filesystem path manipulations
library(survival) # survival analysis
library(survminer) # survival analysis graphics
library(KMsurv) # datasets from Klein and Moeschberger
library(parameters) # format model output tables for
library(webshot2) # convert interactive content to static for pdf
library(forcats) # functions for categorical variables ("factors")
library(stringr) # functions for dealing with strings
library(lubridate) # functions for dealing with dates and times
```

Here are some R settings I use in this document:

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)

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:

2. Linear (Gaussian) Models

- make sure everyone is caught up
- to provide an epidemiological perspective on model interretation.

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
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")))
```

bw

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))
```

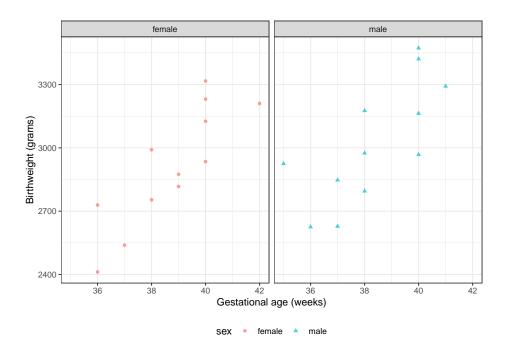


Figure 2.1.: birthweight data (Dobson and Barnett (2018) Example 2.2.2)

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)

2. Linear (Gaussian) Models

- M: indicator variable for $S = \text{``male''}^1$
- 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:

$$p(Y=y|A=a,S=s) \ \sim_{\mathrm{iid}} \ N(\mu(a,s),\sigma^2)$$

 $^{^{1}}M$ is implicitly a deterministic function of S

 $^{^{2}}F$ is implicitly a deterministic function of S

$$\mu(a,s) \stackrel{\text{def}}{=} \mathbb{E}\left[Y|A=a,S=s\right]$$
$$= \beta_0 + \beta_A a + \beta_M m$$
 (2.1)

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 Model 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)
```

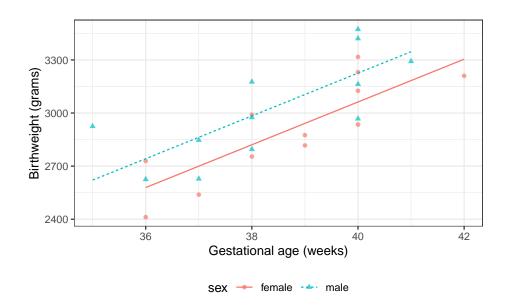


Figure 2.2.: Parallel-slopes model of birthweight

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?

Solution.

$$\begin{split} E[Y|A = 0, A = 36] &= \beta_0 + \beta_M \cdot 0 + \beta_A \cdot 36 \\ &= 2578.8739 \end{split}$$

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

Solution.

$$\begin{split} E[Y|A=1, A=36] &= \beta_0 + \beta_M \cdot 1 + \beta_A \cdot 36 \\ &= 2741.9132 \end{split}$$

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.

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

= 2741.9132 - 2578.8739
= 163.0393

Shortcut:

$$\begin{split} E[Y|A=1,A=36] - E[Y|A=0,A=36] \\ &= (\beta_0 + \beta_M \cdot 1 + \beta_A \cdot 36) - (\beta_0 + \beta_M \cdot 0 + \beta_A \cdot 36) \\ &= \beta_M \\ &= 163.0393 \end{split}$$

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):

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

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 A depends on the value of M.

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.³ 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.

³using the definite article "the" would mean there is only one slope.

$$E[Y|A=0,X_2=36] = \beta_0 + \beta_M \cdot 0 + \beta_A \cdot 36 + \beta_{AM} \cdot (0*36) = 2552.7333$$

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

Solution.

$$\begin{split} E[Y|A=0, X_2=36] &= \beta_0 + \beta_M \cdot 1 + \beta_A \cdot 36 + \beta_{AM} \cdot 1 \cdot 36 \\ &= 2762.7069 \end{split}$$

Exercise 2.6. What's the difference in mean birthweights between males born at 36 weeks and females born at 36 weeks?

40

Solution.

$$\begin{split} E[Y|M=1,A=36] - E[Y|M=0,A=36] \\ &= (\beta_0 + \beta_M \cdot 1 + \beta_A \cdot 36 + \beta_{AM} \cdot 1 \cdot 36) \\ &- (\beta_0 + \beta_M \cdot 0 + \beta_A \cdot 36 + \beta_{AM} \cdot 0 \cdot 36) \\ &= \beta_S + \beta_{AM} \cdot 36 \\ &= 209.9736 \end{split}$$

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:

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

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 β_0 has been relabeled as β_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()
```

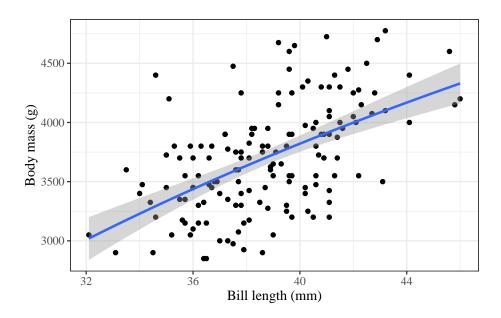


Figure 2.4.: palmerpenguins model with bill_length entering on log scale

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)

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

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

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 β 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 β as input and outputs a scalar, such as $f(\beta) = x'\beta$, then:

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

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

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

In general:

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

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

Similarly,

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

This is like taking the derivative of x^2 .

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

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

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

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

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 β .

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 |> vcov()
#>
                (Intercept)
                             sexmale
                                           age sexmale:age
#> (Intercept)
                   1353968 -1353968 -34871.0
                                                   34871.0
#> sexmale
                   -1353968
                             2596387
                                       34871.0
                                                  -67211.0
                                                     -899.9
#> age
                     -34871
                               34871
                                         899.9
#> 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
$\begin{array}{c} \text{sex (male)} \times \\ \text{age} \end{array}$	-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, σ . We can extract $\hat{\sigma}$ from the fitted model, using the sigma() function:

```
sigma(bw_lm2)
#> [1] 180.6
```

2.3.4.1. σ 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
#> -246.7 -138.1 -39.1 176.6 274.3
#>
#> Coefficients:
              Estimate Std. Error t value Pr(>|t|)
#> (Intercept) -2141.7
                        1163.6
                                  -1.84 0.08057 .
                          1611.3
#> sexmale
               873.0
                                 0.54 0.59395
                130.4
                                   4.35 0.00031 ***
#> age
                            30.0
#> sexmale:age
              -18.4
                            41.8
                                  -0.44 0.66389
#> ---
#> Signif. codes: 0 '***' 0.001 '**' 0.05 '.' 0.1 ' ' 1
```

```
#>
#> Residual standard error: 181 on 20 degrees of freedom
#> Multiple R-squared: 0.643, Adjusted R-squared: 0.59
#> F-statistic: 12 on 3 and 20 DF, p-value: 0.000101
```

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?

$$\begin{split} &H_0: \beta_{AM} = 0 \\ &H_A: \beta_{AM} \neq 0 \\ &P(|\hat{\beta}_{AM}| > |-18.4172| \mid H_0) = ? \end{split}$$

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) sex (male)	$0.00 \\ 872.99$	1611.33	(-2488.18,	0.54	0.594
age	130.40	30.00	4234.17) (67.82, 192.98)	4.35	<
sex (male) × age	-18.42	41.76	(-105.52, 68.68)	-0.44	.001 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)
```

$$\begin{split} &P\left(|\hat{\beta}_{AM}| > |-18.4172| \Big| H_0\right) \\ &= \Pr\left(\left|\frac{\hat{\beta}_{AM}}{\hat{SE}(\hat{\beta}_{AM})}\right| > \left|\frac{-18.4172}{41.7558}\right| \middle| H_0\right) \\ &= \Pr\left(|T_{20}| > 0.4411| H_0\right) \\ &= 0.6639 \end{split}$$

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] 0.6592
```

2.4.7. Confidence intervals

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

Parameter	Coefficient	SE	95% CI	t(20)	р
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] -100.26 63.42
```

2.4.8. Likelihood ratio statistics

```
logLik(bw_lm2)
#> 'log Lik.' -156.6 (df=5)
logLik(bw_lm1)
#> 'log Lik.' -156.7 (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_llR) +
stat_function( fun = d_llR, xlim = c(llR, x_max), geom = "area", fill = "gray") +
geom_segment(aes(x = llR, xend = llR, y = 0, yend = d_llR(llR)), 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*lLR,
    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	-156.6	NA	NA	NA
4	-156.7	-1	0.2323	0.6298

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 ℓ 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] 323.2

AIC(bw_lm2)
#> [1] 323.2
```

2.5.1.2. BIC in R

```
-2 * logLik(bw_lm2) |> as.numeric() +
  (length(coef(bw_lm2))+1) * log(nobs(bw_lm2))
#> [1] 329

BIC(bw_lm2)
#> [1] 329
```

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 (Table 2.14).

```
bw.X.unique
```

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

sex	age	n
female	36	2
female	37	1
female	38	2
female	39	2
female	40	4
female	42	1
male	35	1
male	36	1
male	37	2

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

ge	n
38	3
40	4
41	1
	38 40

Definition 2.1 (Replicates). If a given covariate pattern has more than one observation in a dataset, those observations are called **replicates**.

Example 2.1 (Replicates in the birthweight data). In the birthweight dataset, there are 2 replicates of the combination "female, age 36" (Table 2.14).

Exercise 2.7 (Replicates in the birthweight data). Which covariate pattern(s) in the birthweight data has the most replicates?

Solution 2.1 (Replicates in the birthweight data). Two covariate patterns are tied for most replicates: males at age 40 weeks and females at age 40 weeks. 40 weeks is the usual length for human pregnancy (Polin, Fox, and Abman (2011)), so this result makes sense.

```
bw.X.unique |> dplyr::filter(n == max(n))
```

sex	age	n
female	40	4
male	40	4

2.5.2.1. Saturated models

The most complicated model we could fit would have one parameter (a mean) for each covariate pattern, plus a variance parameter:

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

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

Table 2.16.: 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.' -151.4 (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	-151.4	NA	NA	NA
	5	-156.6	-8	10.36	0.241

The likelihood ratio statistic for this test is

$$\lambda = 2 * (\ell_{\text{full}} - \ell) = 10.3554$$

where:

- $\ell_{\rm max}$ is the log-likelihood of the full model: -151.4016
- ℓ is the log-likelihood of our comparison model (two slopes, two intercepts): -156.5793

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.' -169 (df=2)
```

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

#Df	LogLik	Df	Chisq	Pr(>Chisq)
5	-156.6	NA	NA	NA
2	-169.0	-3	24.75	0

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

$$\lambda=2*(\ell_{\mathrm{full}}-\ell_0)=35.1067$$

where:

- + ℓ_0 is the log-likelihood of the null model: -168.955
- $\ell_{\rm full}$ is the log-likelihood of the maximal model: -151.4016

In R, this test is:

#Df	LogLik	Df	Chisq	Pr(>Chisq)
13	-151.4	NA	NA	NA
2	-169.0	-11	35.11	2e-04

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
(Intercept)	2552.73	97.59	(2349.16, 2756.30)	26.16	< .001
sex (male)	209.97	129.75	(-60.68, 480.63)	1.62	0.121
age - 36 wks	130.40	30.00	(67.82, 192.98)	4.35	< .001
$\begin{array}{l} {\rm sex~(male)} \times {\rm age} \; \text{-} \\ {\rm 36wks} \end{array}$	-18.42	41.76	(-105.52, 68.68)	-0.44	0.664

Compare with what we got without rescaling:

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 2.2 (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 β_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
```

R has built-in functions for prediction:

```
x = tibble(age = 40, sex = "male")
bw_lm1 |> predict(newdata = x)
#> 1
#> 3225
```

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

```
predict(bw_lm1)
      1
                 3
                                                  9
                                                      10
                                                                 12
                                                                       13
                            5
                                                            11
                                                                            14
                                                                                       16
#> 3225 3062 2984 2579 3225 3062 2621 2821 2742 3304 2863 2942 3346 3062 3225 2700
     17
           18
                19
                     20
                           21
                                22
                                      23
                                           24
#> 2863 2579 2984 2821 3225 2942 2984 3062
```

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

Definition 2.3. 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
                                            8
                                                  9
                                                      10
                                                            11
                                                                 12
                                                                       13
                                                                            14
                                                                                  15
                                                                                       16
  3225 3062 2984 2579 3225
                              3062 2621 2821 2742 3304 2863 2942 3346 3062 3225 2700
           18
                19
                     20
                           21
                                22
                                      23
                                           24
     17
#> 2863 2579 2984 2821 3225 2942 2984 3062
```

2.7.3. Quantifying uncertainty in predictions

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

#> $fit

#> 1

#> 3225

#>

#> $se.fit

#> [1] 61.46

#>

#> $df

#> [1] 21

#>

#> $residual.scale

#> [1] 177.1
```

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] 61.46
```

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

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

fit	lwr	upr
3225	3098	3353

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

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

 $\frac{\text{fit} \quad \text{lwr} \quad \text{upr}}{3225 \quad 2836 \quad 3615}$

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



? Tip

This section is adapted from Dobson and Barnett (2018, secs. 6.2-6.3) and Dunn, Smyth, et al. (2018) Chapter 3^a .

^ahttps://link.springer.com/chapter/10.1007/978-1-4419-0118-7_3

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. Homoskedasticity: The variance σ^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 2.4 (Residual noise). The **residual noise** in a probabilistic model p(Y) is the difference between an observed value y and its distributional mean:

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

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

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

Proof. Left to the reader. \Box

Definition 2.5 (Residual errors of a fitted model value). The **residual** of a fitted value \hat{y} (shorthand: "residual") is its error:

$$\begin{aligned} e(\hat{y}) &\stackrel{\text{def}}{=} \epsilon \left(\hat{y} \right) \\ &= y - \hat{y} \end{aligned}$$

 $e(\hat{y})$ 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 2.8:

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

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 σ^2 , which we can estimate using $\hat{\sigma}^2$:

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

that is:

Example 2.2 (residuals in birthweight data). R provides a function for residuals:

```
resid(bw_lm2)
          1
                  2
                           3
                                    4
                                             5
                                                     6
                                                                       8
                                                                                       10
#>
    176.27 -140.73 -144.13
                              -59.53
                                       177.47 -126.93
                                                        -68.93
                                                                 242.67 -139.33
                                                                                    51.67
#>
                          13
                                   14
                                            15
                                                    16
                                                                      18
                                                                                       20
         11
                 12
                                                             17
                                                                               19
#>
    156.67 -125.13
                     274.28
                             -137.71
                                       -27.69 -246.69 -191.67
                                                                 189.33
                                                                          -11.67 -242.64
#>
        21
                 22
                          23
                                   24
    -47.64
           262.36
                     210.36
```

Exercise 2.8. Check R's output by computing the residuals directly.

Solution.

```
bw$weight - fitted(bw_lm2)
        1
                 2
                        3
                                4
                                         5
                                                                 8
                                                                                10
   176.27 -140.73 -144.13 -59.53
#>
                                   177.47 -126.93
                                                   -68.93
                                                            242.67 -139.33
                                                                             51.67
#>
               12
                       13
                               14
                                        15
                                                16
                                                        17
                                                                18
                                                                                20
       11
                                                                        19
#>
   156.67 -125.13 274.28 -137.71
                                   -27.69 -246.69 -191.67
                                                            189.33 -11.67 -242.64
       21
#>
                22
                        23
                                24
   -47.64 262.36 210.36 -30.62
```

This matches R's output!

2.8.3.3. Graph the residuals

```
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 2.6 (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

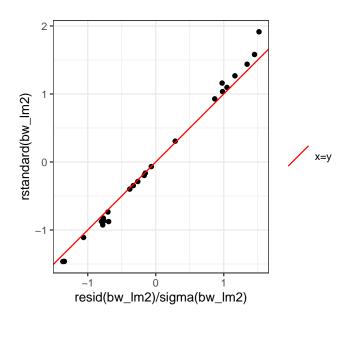
To look for problems with our model, we can check whether the residuals e_i and standardized residuals r_i look like they have the distributions that they are supposed to have, according to the model.

2.8.4.1. Standardized residuals in R

rst	andard(bu	w_lm2)						
#>	1	2	3	4	5	6		7 8
#>	1.15982	-0.92601	-0.87479	-0.34723	1.03507	-0.73473	-0.3990	1 1.43752
#>	9	10	11	12	13	14	1	5 16
#>	-0.82539	0.30606	0.92807	-0.87616	1.91428	-0.86559	-0.1643	0 -1.46376
#>	17	18	19	20	21	22	2	3 24
#>	-1.11016	1.09658	-0.06761	-1.46159	-0.28696	1.58040	1.2671	7 -0.19805
res	sid(bw_lm2	2)/sigma(1	bw_lm2)					
#>	1	2	3	4	5	6		7 8
#>	0.97593	-0.77920	-0.79802	-0.32962	0.98258	-0.70279	-0.3816	6 1.34357
#>	9	10	11	12	13	14	1	5 16
#>	-0.77144	0.28606	0.86741	-0.69282	1.51858	-0.76244	-0.1533	1 -1.36584
#>	17	18	19	20	21	22	2	3 24
#>	-1.06123	1.04825	-0.06463	-1.34341	-0.26376	1.45262	1.1647	1 -0.16954

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	2553	176.27	1.1598
female	36	2412	2553	-140.73	-0.9260
female	37	2539	2683	-144.13	-0.8748
female	38	2754	2814	-59.53	-0.3472
female	38	2991	2814	177.47	1.0351
female	39	2817	2944	-126.93	-0.7347
female	39	2875	2944	-68.93	-0.3990
female	40	3317	3074	242.67	1.4375
female	40	2935	3074	-139.33	-0.8254
female	40	3126	3074	51.67	0.3061
female	40	3231	3074	156.67	0.9281
female	42	3210	3335	-125.13	-0.8762
$_{\mathrm{male}}$	35	2925	2651	274.28	1.9143
$_{\mathrm{male}}$	36	2625	2763	-137.71	-0.8656
$_{\mathrm{male}}$	37	2847	2875	-27.69	-0.1643
$_{\mathrm{male}}$	37	2628	2875	-246.69	-1.4638
$_{\mathrm{male}}$	38	2795	2987	-191.67	-1.1102
$_{\mathrm{male}}$	38	3176	2987	189.33	1.0966
$_{ m male}$	38	2975	2987	-11.67	-0.0676
male	40	2968	3211	-242.64	-1.4616

2. Linear (Gaussian) Models

sex	age	weight	fitted_lm2	resid_lm2	std_resid_lm2
male	40	3163	3211	-47.64	-0.2870
male	40	3473	3211	262.36	1.5804
male	40	3421	3211	210.36	1.2672
male	41	3292	3323	-30.62	-0.1981

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)
```

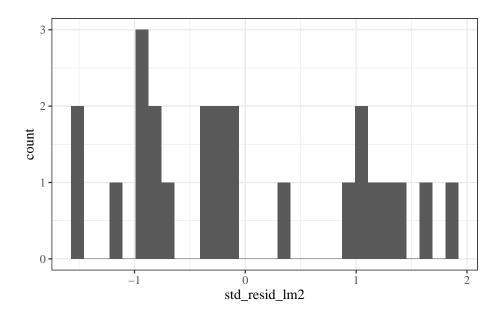


Figure 2.9.: Marginal distribution of standardized residuals

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.

See also Dunn, Smyth, et al. (2018) §3.5.4⁴.

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") +
```

 $^{^4} https://link.springer.com/chapter/10.1007/978-1-4419-0118-7_3\#Sec14:~: text=3.5.4\%20Q\%E2\%80\%93Q\%20Plots\%20and\%20Normality$

```
xlab("Theoretical Quantiles") +
ylab("Standardized residuals")

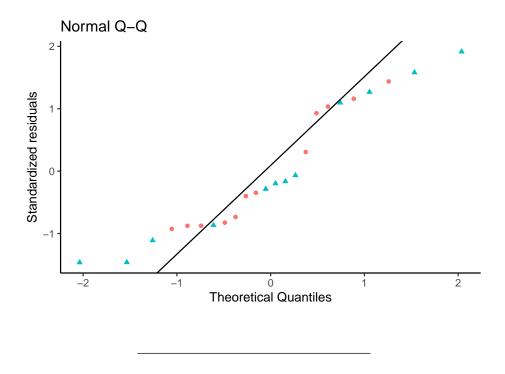
# find the expected line:

ps <- c(.25, .75)  # reference probabilities
a <- quantile(rstandard(bw_lm2), ps) # empirical quantiles
b <- qnorm(ps)  # theoretical quantiles

qq_slope = diff(a)/diff(b)
qq_intcpt = a[1] - b[1] * qq_slope

qqplot_lm2 =
   qqplot_lm2 +
   geom_abline(slope = qq_slope, intercept = qq_intcpt)

print(qqplot_lm2)</pre>
```



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).

Residuals vs Fitted 300 18 22 200 100 Residuals 0 -100-20016 2600 2800 3000 3200 Fitted values

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. Example: PLOS Medicine title length data

(Adapted from Dobson and Barnett (2018), §6.7.1)

```
data(PLOS, package = "dobson")
library(ggplot2)
fig1 =
  PLOS |>
  ggplot(
    aes(x = authors,
        y = nchar)
) +
  geom_point() +
  theme(legend.position = "bottom") +
  labs(col = "") +
  guides(col=guide_legend(ncol=3))
fig1
```



Figure 2.11.: Number of authors versus title length in $PLOS\ Medicine$ articles

Linear fit

```
lm_PLOS_linear = lm(
  formula = nchar ~ authors,
  data = PLOS)
```

```
fig2 = fig1 +
  geom_smooth(
  method = "lm",
      fullrange = TRUE,
```

```
aes(col = "lm(y ~ x)"))
fig2
library(ggfortify)
autoplot(lm_PLOS_linear, which = 1, ncol = 1)
```

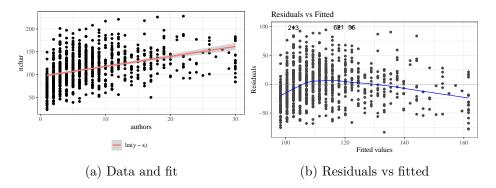


Figure 2.12.: Number of authors versus title length in $PLOS\ Medicine,$ with linear model fit

Quadratic fit

fig2 +
geom_smooth(

method = "lm",

```
lm_PLOS_quad = lm(
  formula = nchar ~ authors + I(authors^2),
  data = PLOS)

fig3 =
```

```
fullrange = TRUE,
  formula = y ~ x + I(x ^ 2),
  aes(col = "lm(y ~ x + I(x^2))")
)
fig3
autoplot(lm_PLOS_quad, which = 1, ncol = 1)
```



Figure 2.13.: Number of authors versus title length in $PLOS\ Medicine,$ with quadratic model fit

Linear versus quadratic fits

```
library(ggfortify)
autoplot(lm_PLOS_linear, which = 1, ncol = 1)
autoplot(lm_PLOS_quad, which = 1, ncol = 1)
```



Figure 2.14.: Residuals versus fitted plot for linear and quadratic fits to PLOS data

Cubic fit

```
lm_PLOS_cub = lm(
  formula = nchar ~ authors + I(authors^2) + I(authors^3),
  data = PLOS)
```

```
fig4 =
  fig3 +
geom_smooth(
    method = "lm",
    fullrange = TRUE,
    formula = y ~ x + I(x ^ 2) + I(x ^ 3),
    aes(col = "lm(y ~ x + I(x^2) + I(x ^ 3))")
)
fig4
autoplot(lm_PLOS_cub, which = 1, ncol = 1)
```

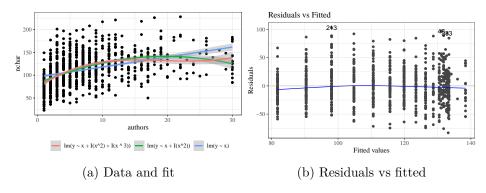


Figure 2.15.: Number of authors versus title length in PLOS Medicine, with cubic model fit

Logarithmic fit

```
lm_PLOS_log = lm(nchar ~ log(authors), data = PLOS)
```

```
fig5 = fig4 +
  geom_smooth(
    method = "lm",
    fullrange = TRUE,
    formula = y ~ log(x),
    aes(col = "lm(y ~ log(x))")
)
fig5
autoplot(lm_PLOS_log, which = 1, ncol = 1)
```

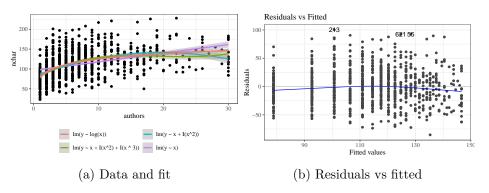


Figure 2.16.: logarithmic fit

Model selection

anova(lm_PLOS_linear, lm_PLOS_quad)

Table 2.26.: linear vs quadratic

Res.Df	RSS	Df	Sum of Sq	F	Pr(>F)
876	947502	NA	NA	NA	NA
875	880950	1	66552	66.1	0

anova(lm_PLOS_quad, lm_PLOS_cub)

Table 2.27.: quadratic vs cubic

Res.Df	RSS	Df	Sum of Sq	F	Pr(>F)
875	880950	NA	NA	NA	NA
874	865933	1	15018	15.16	1e-04

AIC/BIC

```
AIC(lm_PLOS_quad)

#> [1] 8568

AIC(lm_PLOS_cub)

#> [1] 8555

AIC(lm_PLOS_cub)

#> [1] 8555

AIC(lm_PLOS_log)

#> [1] 8544
```

```
BIC(lm_PLOS_cub)

#> [1] 8578

BIC(lm_PLOS_log)

#> [1] 8558
```

Extrapolation is dangerous

```
fig_all = fig5 +
   xlim(0, 60)
fig_all
```

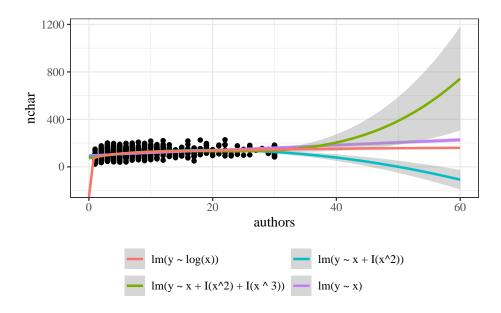


Figure 2.17.: Number of authors versus title length in $PLOS\ Medicine$

2.8.6.3. Scale-location plot

We can also plot the square roots of the absolute values of the standardized residuals against the fitted values (Figure 2.18).

autoplot(bw_lm2, which = 3, ncol = 1) |> print()

Figure 2.18.: 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 σ^2 might not be constant, and we might need to transform our outcome Y (or use a model that allows non-constant variance).

2.8.6.4. 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.



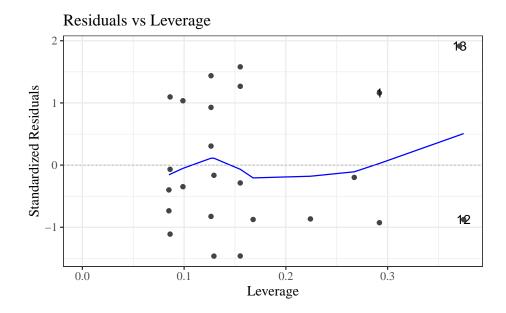


Figure 2.19.: birthweight model with interactions (Equation 2.2): residuals versus leverage

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

(adapted from Dobson and Barnett (2018) §6.3.3; for more information on prediction, see James et al. (2013) and Harrell (2015)).

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**, $E[(y-\hat{y})^2]$, for new observations that weren't in our data set when we fit the model.

Unfortunately,

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

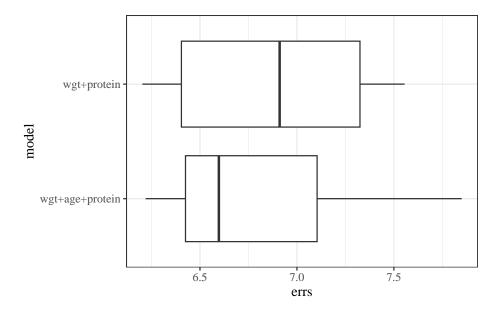
gives a biased estimate of $\mathrm{E}[(y-\hat{y})^2]$ for new data. If we want an unbiased estimate, we will have to be clever.

2.9.1.1. Cross-validation

```
results_reduced =
  tibble(
    model = "wgt+protein",
    errs = cv_reduced$reps[])
results_full =
  tibble(model = "wgt+age+protein",
        errs = cv_full$reps[])

cv_results =
  bind_rows(results_reduced, results_full)

cv_results |>
  ggplot(aes(y = model, x = errs)) +
  geom_boxplot()
```



comparing metrics

```
compare_results = tribble(
    ~ model, ~ cvRMSE, ~ r.squared, ~adj.r.squared, ~ trainRMSE, ~loglik,
    "full", cv_full$cv, summary(full_model)$r.squared, summary(full_model)$adj.r.squared,
    "reduced", cv_reduced$cv, summary(reduced_model)$r.squared, summary(reduced_model)
compare_results
```

model	cvRMSE	r.squared	adj.r.squared	trainRMSE	loglik
full	6.795	0.4805	0.3831	5.956	-61.84
reduced	6.868	0.4454	0.3802	5.971	-62.49

anova(full_model, reduced_model)

Res.Df	RSS	Df	Sum of Sq	F	Pr(>F)
16	567.7	NA	NA	NA	NA
17	606.0	-1	-38.36	1.081	0.3139

2.9.1.2. stepwise regression

:>	ols_step_both_ai	c(full_mode	1)			
;> ;>		Ste	pwise Summa	ry		
_	Variable	AIC	SBC	SBIC	R2	Adj. R2
> 1	Base Model protein (+) weight (+)	137.950	140.937	80.438	0.21427	0.17061
	Model Output					
:> :>		Model S	•			
> R > R-Square > Adj. 1	ared R-Squared R-Squared	0.667 0.445 0.380	RMSE MSE Coef. V AIC	ar	5.505 35.648 15.879 132.981 136.964	
> > RMSE > MSE: > MAE: > AIC:		are Error for Crror cion Criteri			100.004	
:>		A	NOVA			
;> ;>	 Sum c					

#>		Squares	DF M	lean Square	F	Sig.	
#>							
#>	Regression	486.778	2	243.389	6.827	0.0067	
#>	Residual	606.022	17	35.648			
#>	Total	1092.800	19				
#>							
#>							
#>			Par	ameter Estim	ates		
#>							
#>	model	Beta	Std. Error	Std. Beta	t	Sig	lower
#>							
#>	(Intercept)	33.130	12.572		2.635	0.017	6.607
#>	protein	1.824	0.623	0.534	2.927	0.009	0.509
#>	weight	-0.222	0.083	-0.486	-2.662	0.016	-0.397
#>							

2.9.1.3. Lasso

$$\arg \min_{\theta} \ell(\theta) + \lambda \sum_{j=1}^p |\beta_j|$$

```
library(glmnet)
y = carbohydrate$carbohydrate
x = carbohydrate |>
    select(age, weight, protein) |>
    as.matrix()
fit = glmnet(x,y)
```

autoplot(fit, xvar = 'lambda')

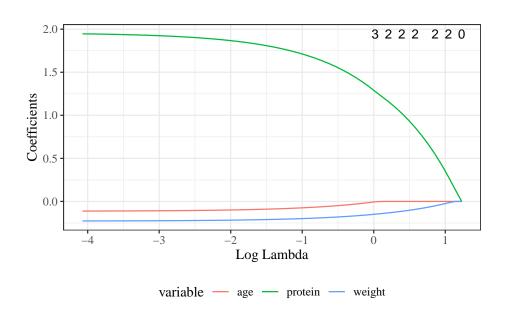
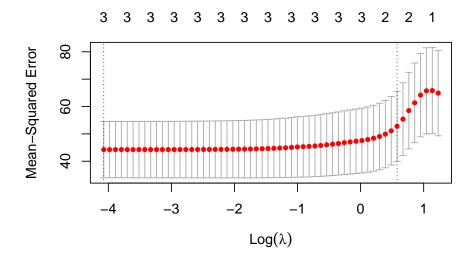


Figure 2.20.: Lasso selection

```
cvfit = cv.glmnet(x,y)
plot(cvfit)
```



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 2.30 shows the (in)famous⁵ iris data (Anderson (1935)), and Table 2.31 provides summary statistics. The data include three species: "setosa", "versicolor", and "virginica".

head(iris)

Table 2.30.: The iris data

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

⁵https://www.meganstodel.com/posts/no-to-iris/

Table 2.30.: The iris data

Sepal.Length	Sepal.Width	Petal.Length	Petal.Width	Species
4.6	3.1	1.5		setosa
5.0 5.4	$\frac{3.6}{3.9}$	$\frac{1.4}{1.7}$		setosa setosa

```
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 =
  iris |>
  tibble() |>
  mutate(
    X = case_when(
        Species == "setosa" ~ 1,
        Species == "virginica" ~ 2,
        Species == "versicolor" ~ 3
```

Table 2.31.: 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]

```
iris |>
distinct(Species, X)
```

Table 2.32.: iris data with numeric coding of species

Species	X
setosa	1
versicolor	3
virginica	2

Then we could fit a model like:

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

Table 2.33.: Model of iris data with numeric coding of Species

Parameter	Coefficient	SE	95% CI	t(148)	p
(Intercept)	4.91	0.16	(4.60, 5.23)	30.83	< .001
X	0.47	0.07	(0.32, 0.61)	6.30	< .001

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)
```

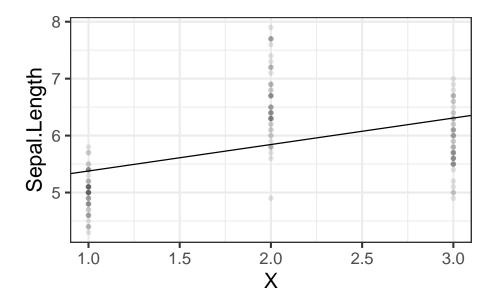


Figure 2.21.: Model of iris data with numeric coding of Species

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()
```

Table 2.34.: Model of iris data with Species as a categorical variable

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:

```
iris.lm2b = lm(Sepal.Length ~ Species - 1, data = iris)
iris.lm2b |> parameters() |> print_md()
```

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



Figure 2.22.

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".

```
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 package⁶ vignette⁷ (Venables (2023)).

2.11. Ordinal covariates

(c.f. Dobson and Barnett (2018) §2.4.4)

We can create ordinal variables in R using the ordered() function⁸.

Example 2.3.

⁶https://CRAN.R-project.org/package=codingMatrices

 $^{^{7}} https://cran.r-project.org/web/packages/codingMatrices/vignettes/codingMatrices. \\pdf$

⁸ or equivalently, factor(ordered = TRUE)

```
url = paste0(
   "https://regression.ucsf.edu/sites/g/files/tkssra6706/",
   "f/wysiwyg/home/data/hersdata.dta")
library(haven)
hers = read_dta(url)

hers |> head()
```

Table 2.38.: HERS dataset

Η	Tag c a	ae	blan	мфі	kidaa	l g ad	a igl	ealo	tei	cebali	ioseti	adi	hb	eitp	ishkiightalatellaveightalatellatedkaliH DIGcHa lHDIG BIBBge10
0	702	1	0	0	0	5	3	0	0	1	1	0	0	0	73 2 3 95 00.9 3 273 2 3 953 0.99218 9222 47320 1 3 7 87713 7 87.0
0	622	1	0	0	0	1	3	0	1	1	0	0	0	0	70 28 56 200 96 447 3 218 38 300 97 84 30 72 4 14 46 10 72 16 56 48 88 7 11 87 0 6 . 2
1	691	0	0	0	0	3	3	0	0	1	0	1	0	0	10 2/205110.7829 6/40. 7330.038 2546 6.2 15 2 545 6 .6016 0 34786.9
0	641	0	1	1	0	1	3	0	1	1	0	0	0	0	64 24\$700874 58 22.7520892 2041 5.2 15 2 0 722.7 513 7 5 7 26.4
0	651	0	0	0	0	2	3	0	0	0	0	0	0	0	57 2 0.7900.790458 2 2.72805.73272145042610 2 3 5 7 2 2139.7 9 56.5
1	682	1	0	1	0	3	3	0	0	0	0	0	0	0	60 2 9 9 50 00057 2 7 5 620 9110 2 12 3 7 2 311202 26 5112 74 86.8

```
# C(contr = codingMatrices::contr.diff)
```

Logistic regression and variations



Configuring R

Functions from these packages will be used throughout this document:

```
library(conflicted) # check for conflicting function definitions
# library(printr) # inserts help-file output into markdown output
library(rmarkdown) # Convert R Markdown documents into a variety of formats.
library(pander) # format tables for markdown
library(ggplot2) # graphics
library(ggeasy) # help with graphics
library(ggfortify) # help with graphics
library(dplyr) # manipulate data
library(tibble) # `tibble`s extend `data.frame`s
library(magrittr) # `%>%` and other additional piping tools
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(haven) # import Stata files
library(latex2exp) # use LaTeX in R code (for figures and tables)
library(fs) # filesystem path manipulations
library(survival) # survival analysis
library(survminer) # survival analysis graphics
library(KMsurv) # datasets from Klein and Moeschberger
library(parameters) # format model output tables for
library(webshot2) # convert interactive content to static for pdf
library(forcats) # functions for categorical variables ("factors")
library(stringr) # functions for dealing with strings
library(lubridate) # functions for dealing with dates and times
```

Here are some R settings I use in this document:

```
pander::panderOptions("table.split.table", Inf)
conflicts_prefer(dplyr::filter) # use the `filter()` function from dplyr() by defaul
legend_text_size = 9
```

Acknowledgements

This content is adapted from:

- Dobson and Barnett (2018), Chapter 7
- Vittinghoff et al. (2012), Chapter 5
- David Rocke¹'s materials from the 2021 edition of Epi 204²

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:

¹https://dmrocke.ucdavis.edu/

²https://dmrocke.ucdavis.edu/Class/EPI204-Spring-2021/EPI204-Spring-2021.html

- 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. The **Bernoulli distribution** family for a random variable X is defined as:

$$\begin{split} \Pr(X = x) &= \mathbb{1}_{x \in \{0,1\}} \pi^x (1 - \pi)^{1 - x} \\ &= \left\{ \begin{matrix} \pi, x = 1 \\ 1 - \pi, x = 0 \end{matrix} \right. \end{split}$$

129

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.

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

Solution.

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

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

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

```
library(dplyr)
oc_mi =
 tribble(
   ~OC, ~MI, ~Total,
   "OC use", 13, 5000,
   "No OC use", 7, 10000
 ) |>
 mutate(`No MI` = Total - MI) |>
 relocate(`No MI`, .after = MI)
totals =
 oc_mi |>
 summarize(across(c(MI, `No MI`, Total), sum)) |>
 mutate(OC = "Total")
tbl_oc_mi = bind_rows(oc_mi, totals)
tbl_oc_mi
#> # A tibble: 3 x 4
#>
   OC
          MI `No MI` Total
#> <chr>
            <dbl> <dbl> <dbl>
#> 1 OC use 13
                    4987 5000
#> 2 No OC use
                7
                     9993 10000
#> 3 Total 20 14980 15000
```

3.2.0.1. Controls

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**.

3.3. Comparing probabilities

3.3.1. Risk differences

The simplest comparison of two probabilities, π_1 , and π_2 , is the difference of their values:

Definition 3.3 (Risk difference). The **risk difference** of two probabilities, π_1 , and π_2 , is the difference of their values:

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

Example 3.2 (Difference in MI risk). In Example 3.1, the maximum likelihood estimate of the difference in MI risk between OC users and OC non-users is:

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

3.3.2. Risk ratios

Definition 3.4 (Relative risk ratios).

The **relative risk** of probability π_1 compared to another probability π_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:

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

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

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

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

$$\begin{split} \hat{\rho}(OC, \neg OC) &= \frac{\hat{\mathbf{p}}(MI|OC)}{\hat{\mathbf{p}}(MI|\neg OC)} \\ &= \frac{0.0026}{7 \times 10^{-4}} \\ &= 3.7143 \end{split}$$

We might summarize this result by saying that "the estimated probability of MI among OC users was 3.7143 as high as the estimated probability among OC non-users.

3.3.3. Relative risk difference

Definition 3.5 (Relative risk difference).

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**:

$$\begin{split} \xi(\pi_1, \pi_2) & \stackrel{\text{def}}{=} \frac{\delta(\pi_1, \pi_2)}{\pi_2} \\ & = \frac{\pi_1 - \pi_2}{\pi_2} \\ & = \frac{\pi_1}{\pi_2} - 1 \\ & = \rho(\pi_1, \pi_2) - 1 \end{split}$$

3.3.3.1. Changing reference groups in risk comparisons

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).

$$\delta(\pi_2,\pi_1) = -\delta(\pi_1,\pi_2)$$

$$\begin{split} \rho(\pi_2, \pi_1) &= \left(\rho(\pi_1, \pi_2)\right)^{-1} \\ \xi(\pi_2, \pi_1) &= \left(\xi(\pi_2, \pi_1) + 1\right)^{-1} - 1 \end{split}$$

Exercise 3.5. Prove the relationships above.

Example 3.4 (Switching the reference group in a risk ratio). Above, we estimated that the risk ratio of OC versus non-OC is:

$$\rho(OC, \neg OC) = 3.7143$$

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

$$\begin{split} \rho(\neg OC, OC) &= \frac{\hat{\mathbf{p}}(MI|\neg OC)}{\hat{\mathbf{p}}(MI|OC)} \\ &= \frac{7\times 10^{-4}}{0.0026} \\ &= 0.2692 \\ &= \frac{1}{\rho(OC, \neg OC)} \end{split}$$

3.3.4. Odds and probabilities

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

Definition 3.6 (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:

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

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

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

Proof.

$$\Pr(\neg A) = 1 - \Pr(A)$$
$$= 1 - \pi$$

Function 3.1, which transforms probabilities into odds, can be called the **odds function**. Figure 3.1 graphs the shape of this function.

```
theme_bw() +
labs(colour = "") +
theme(legend.position = "bottom")
```

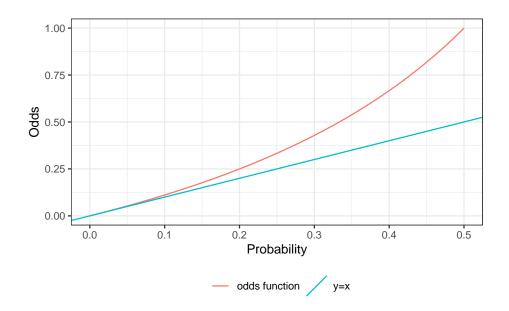


Figure 3.1.: Odds versus probability

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:

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

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

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

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

$$\approx 0.002607$$

Exercise 3.6 (Calculating odds). Estimate the odds of MI, for non-OC users.

Solution.

$$\omega(\neg OC) = 7.0049 \times 10^{-4}$$

Theorem 3.2 (One-sample MLE for odds). Let $X_1,...X_n$ be a set of n iid Bernoulli trials, and let $X = \sum_{i=1}^n X_i$ be their sum.

Then the maximum likelihood estimate of the odds of X = 1, ω , is:

$$\hat{\omega} = \frac{x}{n - x}$$

Proof.

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

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

$$\omega(OC) = 0.0026$$

Let's recalculate this result using our shortcut.

Solution 3.1.

$$\omega(OC) = \frac{13}{5000 - 13} \\ = 0.0026$$

Same answer as in Example 3.5!

3.3.4.1. Odds of rare events

For rare events (small π), 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 6.7776×10^{-6} .

Exercise 3.7. What odds value corresponds to the probability $\pi = 0.2$, and what is the numerical difference between these two values?

Solution.

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

3.3.5. The inverse odds function

Definition 3.7 (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"))
```

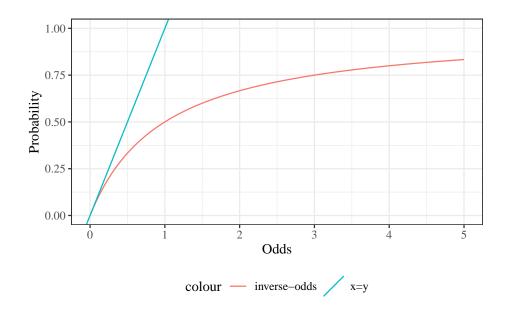


Figure 3.2.: The inverse odds function, $\pi(\omega)$

! Important

An equivalent expression for the inverse odds function is

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

Exercise 3.8. Prove that Equation 3.2 is equivalent to Definition 3.7.

Exercise 3.9. What probability corresponds to an odds of $\omega = 1$, and what is the numerical difference between these two values?

Solution.

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

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

3.3.6. Odds ratios

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

Definition 3.8 (Odds ratio). The **odds ratio** for two odds ω_1 , ω_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:

$$\theta(\omega(OC), \omega(\neg OC)) = \frac{\omega(OC)}{\omega(\neg OC)}$$
$$= \frac{0.0026}{7 \times 10^{-4}}$$
$$= 3.7143$$

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.

3.3.6.1. 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
Exposed	a	b	a+b
Non-exposed	\mathbf{c}	d	c+d
Total	a+c	b+d	a+b+c+d

From this table, we have:

- $\bullet \ \ \widehat{\pi}(Event|Exposed) = a/(a+b)$
- $\hat{\pi}(\neg Event|Exposed) = b/(a+b)$
- $\hat{\omega}(Event|Exposed) = \frac{\left(\frac{a}{a+b}\right)}{\left(\frac{b}{a+b}\right)} = \frac{a}{b}$
- $\hat{\omega}(Event|\neg Exposed) = \frac{c}{d}$ (see Exercise 3.10)
- $\theta(Exposed, \neg Exposed) = \frac{\frac{a}{b}}{\frac{c}{d}} = \frac{ad}{bc}$

Exercise 3.10. Given Table 3.2, show that $\hat{\omega}(Event|\neg Exposed) = \frac{c}{d}$.

146

3.4. 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.

Theorem 3.3 (Odds ratios are reversible). For any two events A, B:

$$\theta(A|B) = \theta(B|A)$$

Proof.

$$\theta(A|B) \stackrel{\text{def}}{=} \frac{\omega(A|B)}{\omega(A|\neg B)}$$

$$= \frac{\left(\frac{p(A|B)}{p(\neg A|B)}\right)}{\left(\frac{p(A|\neg B)}{p(\neg A|\neg B)}\right)}$$

$$= \left(\frac{p(A|B)}{p(\neg A|B)}\right) \left(\frac{p(A|\neg B)}{p(\neg A|\neg B)}\right)^{-1}$$

$$= \left(\frac{p(A|B)}{p(\neg A|B)}\right) \left(\frac{p(\neg A|\neg B)}{p(A|\neg B)}\right)$$

$$= \left(\frac{p(A|B)}{p(\neg A|B)} \cdot \frac{p(B)}{p(B)}\right) \left(\frac{p(\neg A|\neg B)}{p(A|\neg B)} \cdot \frac{p(\neg B)}{p(\neg B)}\right)$$

$$= \left(\frac{p(A,B)}{p(\neg A,B)}\right) \left(\frac{p(\neg A,\neg B)}{p(A,\neg B)}\right)$$

$$= \left(\frac{p(B,A)}{p(B,\neg A)}\right) \left(\frac{p(\neg B,\neg A)}{p(\neg B,A)}\right)$$

$$= \left(\frac{p(B,A)}{p(\neg B,A)}\right) \left(\frac{p(\neg B,\neg A)}{p(B,\neg A)}\right)$$

$$= [\text{reverse the preceding steps}]$$

$$= \theta(B|A)$$

Conditional odds ratios have the same reversibility property:

Theorem 3.4 (Conditional odds ratios are reversible). For any three events A, B, C:

$$\theta(A|B,C) = \theta(B|A,C)$$

Proof. Apply the same steps as for Theorem 3.3, inserting C into the conditions (RHS of |) of every expression.

Example 3.8. In Example 3.1, we have:

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

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

$$= \frac{\left(\frac{\Pr(MI,OC)}{\Pr(\neg MI,OC)}\right)}{\left(\frac{\Pr(MI,OC)}{\Pr(\neg MI,OC)}\right)}$$

$$= \left(\frac{\Pr(MI,OC)}{\Pr(\neg MI,OC)}\right) \left(\frac{\Pr(\neg MI,\neg OC)}{\Pr(MI,\neg OC)}\right)$$

$$= \left(\frac{\Pr(MI,OC)}{\Pr(MI,\neg OC)}\right) \left(\frac{\Pr(\neg MI,\neg OC)}{\Pr(\neg MI,OC)}\right)$$

$$= \left(\frac{\Pr(OC,MI)}{\Pr(\neg OC,MI)}\right) \left(\frac{\Pr(\neg OC,\neg MI)}{\Pr(OC,\neg MI)}\right)$$

$$= \left(\frac{\Pr(OC|MI)}{\Pr(\neg OC|MI)}\right) \left(\frac{\Pr(\neg OC|\neg MI)}{\Pr(OC|\neg MI)}\right)$$

$$= \frac{\left(\frac{\Pr(OC|MI)}{\Pr(\neg OC|MI)}\right)}{\left(\frac{\Pr(OC|\neg MI)}{\Pr(\neg OC|\rightarrow MI)}\right)}$$

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

$$\stackrel{\text{def}}{=} \theta(OC;MI)$$

Exercise 3.11. For Table 3.2, show that $\hat{\theta}(Exposed, Unexposed) = \hat{\theta}(Event, \neg Event).$

3.4.1. Case-Control Studies

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 3.4:

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

Exercise 3.12. 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.

• $\omega(OC|MI) = P(OC|MI)/(1-P(OC|MI) = \frac{13}{7} = 1.8571$

•
$$\omega(OC|\neg MI) = P(OC|\neg MI)/(1-P(OC|\neg MI) = \frac{4987}{9993} = 0.499$$

•
$$\theta(OC, MI) = \frac{\omega(OC|MI)}{\omega(OC|\neg MI)} = \frac{13/7}{4987/9993} = 3.7214$$

This is the same estimate we calculated in Example 3.7.

3.4.2. 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.

3.5. 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.

3.5.1. Binary outcomes models - one group, no covariates

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

3.5.2. Binary outcomes - general

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

3.5.3. Modeling π_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 3.9 (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)
```

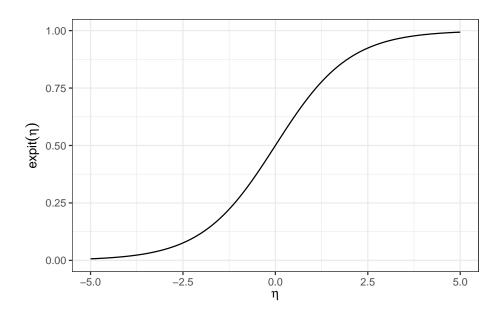


Figure 3.3.: The expit function

Definition 3.10 (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)
```

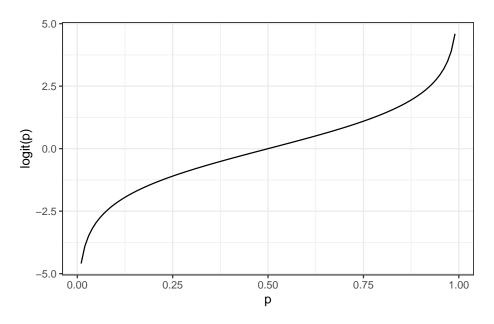


Figure 3.4.: the logit function

3.5.4. Diagram of expit and logit

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

3.5.5. 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)
```

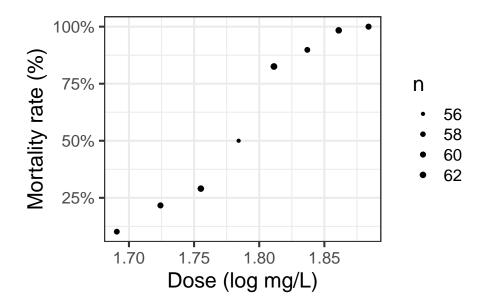


Figure 3.5.: Mortality rates of adult flour beetles after five hours' exposure to gaseous carbon disulphide (Bliss 1935)

3.5.6. Why don't we use linear regression?

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

lm1 = beetles_long |> lm(formula = outcome ~ dose)
f.linear = function(x) predict(lm1, newdata = data.frame(dose = x))
```

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

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

plot2 |> print()
```

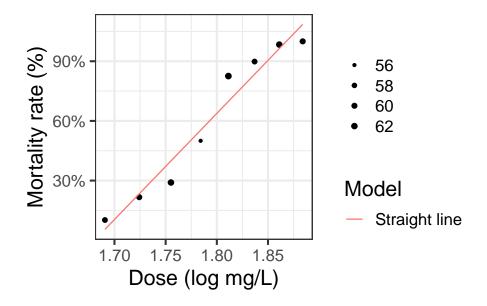


Figure 3.6.: Mortality rates of adult flour beetles after five hours' exposure to gaseous carbon disulphide (Bliss 1935)

3.5.7. Zoom out





Figure 3.7.: Mortality rates of adult flour beetles after five hours' exposure to gaseous carbon disulphide (Bliss 1935)

3.5.8. log transformation of dose?

```
lm2 = beetles_long |> lm(formula = outcome ~ log(dose))
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"))
(plot3 + expand_limits(x = c(1.6, 2))) |> print()
```

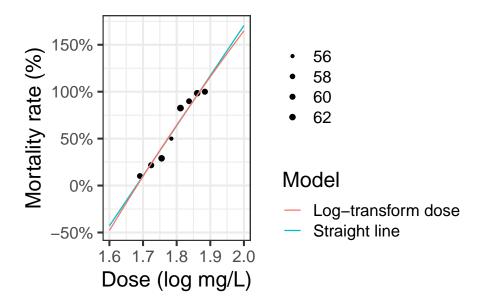
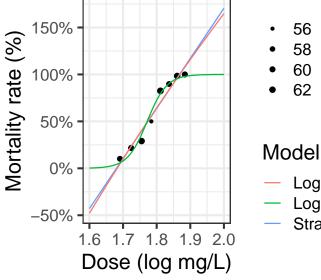


Figure 3.8.: Mortality rates of adult flour beetles after five hours' exposure to gaseous carbon disulphide (Bliss 1935)

3.5.9. Logistic regression

```
#| label: fig-beetles_5
#| fig-cap: "Mortality rates of adult flour beetles after five hours' exposure to ga
beetles_glm_grouped = beetles |>
```

```
glm(formula = cbind(died, survived) ~ dose, family = "binomial")
f = function(x)
  beetles_glm_grouped |>
  predict(newdata = data.frame(dose = x), type = "response")
plot4 = plot3 + geom_function(fun = f, aes(col = "Logistic regression"))
plot4 |> print()
```



- 58
- 60

- Log-transform dose
- Logistic regression
- Straight line

3.5.10. 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)

3.5.11. Logistic regression in R

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

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

Parameter	Log-Odds	SE	95% CI	${f z}$	p
(Intercept)	-60.72		(-71.44, -51.08)		
dose	34.27	2.91	(28.85, 40.30)	11.77	< .001

Fitted values:

```
fitted.values(beetles_glm_grouped)
#> 1 2 3 4 5 6 7 8
#> 0.0586 0.1640 0.3621 0.6053 0.7952 0.9032 0.9552 0.9790
predict(beetles_glm_grouped, type = "response")
#> 1 2 3 4 5 6 7 8
#> 0.0586 0.1640 0.3621 0.6053 0.7952 0.9032 0.9552 0.9790
predict(beetles_glm_grouped, type = "link")
#> 1 2 3 4 5 6 7 8
#> -2.7766 -1.6286 -0.5662 0.4277 1.3564 2.2337 3.0596 3.8444
fit_y = beetles$n * fitted.values(beetles_glm_grouped)
```

3.5.12. Individual observations

```
beetles_glm_ungrouped =
  beetles_long |>
  glm(
    formula = outcome ~ dose,
    family = "binomial")

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

Table 3.4.: beetles data in long format

bee	etle	s_long	ŗ						
		tibb		1 x 6					
#>		dose	died	L	n	pct	survived	outcome	
#>		<dbl></dbl>	<int></int>	<int< td=""><td>></td><td><dbl></dbl></td><td><int></int></td><td><dbl></dbl></td><td></td></int<>	>	<dbl></dbl>	<int></int>	<dbl></dbl>	
#>	1	1.69	6	5 5	9	0.102	53	1	
#>	2	1.69	6	5 5	9	0.102	53	1	
#>	3	1.69	6	5 5	9	0.102	53	1	
#>	4	1.69	6	5 5	9	0.102	53	1	
#>	5	1.69	6	5 5	9	0.102	53	1	
#>	6	1.69	6	5 5	9	0.102	53	1	
#>	7	1.69	6	5 5	9	0.102	53	0	
#>	8	1.69	6	5 5	9	0.102	53	0	
#>	9	1.69	6	5	9	0.102	53	0	
#>	10	1.69	6	5 5	9	0.102	53	0	
#>	# i	. 471 n	nore r	OWS					

Table 3.5.: logistic regression model for beetles data with individual Bernoulli data

Parameter	Log-Odds	SE	95% CI	Z	p
(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()
```

Table 3.6.: logistic regression model for beetles data with grouped (binomial) data

Parameter	Log-Odds	SE	95% CI	Z	р
(Intercept)	-60.72	5.18	(-71.44, -51.08)	-11.72	< .001
dose	34.27	2.91	(28.85, 40.30)	11.77	< .001

They seem the same! But not quite:

```
logLik(beetles_glm_grouped)
#> 'log Lik.' -18.72 (df=2)
logLik(beetles_glm_ungrouped)
#> 'log Lik.' -186.2 (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.

3.6. Multiple logistic regression

3.6.1. Coronary heart disease (WCGS) study data

Let's use the data from the Western Collaborative Group Study (WCGS) (Rosenman et al. (1975)) to explore multiple logistic regression:

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)".

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."

3.6.1.1. 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::wcgs)

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.

3.6.2. Baseline data collection

socio-demographic characteristics:

- age
- education
- marital status
- income
- occupation
- physical and physiological including:
- height
- weight
- blood pressure
- electrocardiogram
- · corneal arcus;

biochemical measurements: - cholesterol and lipoprotein fractions; - medical and family history and use of medications;

behavioral data:

- 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.

3.6.3. Load the data

Here, I load the data:

```
### load the data directly from a UCSF website:
library(haven)
url = paste0(
    # I'm breaking up the url into two chunks for readability
    "https://regression.ucsf.edu/sites/g/files/",
    "tkssra6706/f/wysiwyg/home/data/wcgs.dta")
wcgs = haven::read_dta(url)
```

Table 3.7.: wcgs data

```
wcgs |> head()
#> # A tibble: 6 x 22
       age arcus behpat
                          bmi chd69 chol
                                            dbp dibpat height
                                                                 id lnsbp lnwght
#>
     <dbl> <lgl> <fct> <dbl> <fct> <dbl> <fct> <dbl> <fct>
                                                        <dbl> <dbl> <dbl>
                                                                           <dbl>
#> 1
       50 TRUE A1
                                                           67 2343 4.88
                                                                             5.30
                         31.3 No
                                      249
                                             90 Type A
#> 2
       51 FALSE A1
                         25.3 No
                                      194
                                             74 Type A
                                                           73 3656 4.79
                                                                            5.26
#> 3
       59 TRUE A1
                         28.7 No
                                      258
                                             94 Type A
                                                           70 3526 5.06
                                                                            5.30
#> 4
     51 TRUE A1
                                             80 Type A
                                                           69 22057 4.84
                                                                            5.01
                         22.1 No
                                      173
#> 5
       44 FALSE A1
                         22.3 No
                                      214
                                             80 Type A
                                                           71 12927 4.84
                                                                            5.08
#> 6
     47 FALSE A1
                         27.1 No
                                      206
                                             76 Type A
                                                           64 16029 4.75
                                                                            5.06
#> # i 10 more variables: ncigs <dbl>, sbp <dbl>, smoke <fct>, t1 <dbl>,
       time169 <dbl>, typchd69 <fct>, uni <dbl>, weight <dbl>, wghtcat <fct>,
#> #
       agec <fct>
```

3.6.4. Data cleaning

Now let's do some data cleaning

```
library(arsenal) # provides `set_labels()`
library(forcats) # provides `as_factor()`

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)
```

3.6.5. 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 3.8.: Baseline characteristics by CHD status at end of follow-up

	3.7	3.7	- TD + 1	
	No	Yes	Total	p
	(N=2897)	(N=257)	(N=3154)	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	
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%)	

 $3.\ Models\ for\ Binary\ Outcomes$

	No	Yes	Total	p
	(N=2897)	(N=257)	(N=3154)	value
B4	331	18 (7.0%)	349	
	(11.4%)	,	(11.1%)	
Body Mass Index	,		,	<
$(\mathrm{kg/m2})$				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}
Mean (SD)	81.723	85.315	82.016	
	(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)	

	No (N=2897)	Yes (N=257)	Total (N=3154)	p value
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)	
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%)	

	No (N. 2007)	Yes	Total	р
	(N=2897)	(N=257)	(N=3154)	value
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}
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%)	

	No	Yes	Total	p
	(N=2897)	(N=257)	(N=3154)	value
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

3.6.6. 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
#> # A tibble: 42 x 6
      #>
    <dbl> <fct> <int> <dbl+lbl>
                                <dbl>
                                            <dbl>
   1
       50 Type A 76 0.105
                                0.118
                                            -2.14
#>
               67 0.164
#>
  2
      51 Type A
                                0.196
                                            -1.63
#> 3 59 Type A
               30 0.233
                                            -1.19
                                0.304
#> 4 44 Type A
               113 0.0796
                                0.0865
                                            -2.45
#> 5 47 Type A
               72 0.0972
                                0.108
                                            -2.23
               133 0.0677
#> 6
      40 Type A
                                0.0726
                                            -2.62
#> 7 41 Type A
               108 0.0648
                                0.0693
                                            -2.67
#> 8
      43 Type A
                97 0.0722
                                0.0778
                                            -2.55
#> 9
       54 Type A
                 53 0.132
                                0.152
                                            -1.88
#> 10
      48 Type A
                80 0.15
                                0.176
                                            -1.73
#> # i 32 more rows
```

3.6.7. Graphical exploration

```
library(ggplot2)
library(ggeasy)
library(scales)
chd_plot_probs =
   chd_grouped_data |>
   ggplot(
    aes(
     x = age,
     y = `p(chd)`,
     col = dibpat)
) +
```



Figure 3.9.: CHD rates by age group, probability scale

3.6.7.1. Odds scale

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

chd_plot_odds = chd_plot_probs +
  scale_y_continuous(
    trans = trans_odds, # this line changes the vertical spacing
```



Figure 3.10.: CHD rates by age group, odds spacing

3.6.7.2. 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)
```

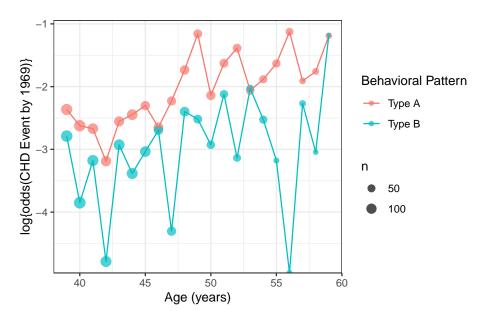


Figure 3.11.: CHD data (logit-scale)

3.6.8. 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()
```

Table 3.9.: CHD model, stratified parametrization

	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 3.10.: 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
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					

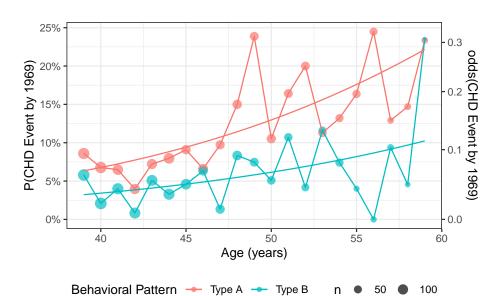
3.6.9. Models superimposed on data

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

3.6.9.1. 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)
```

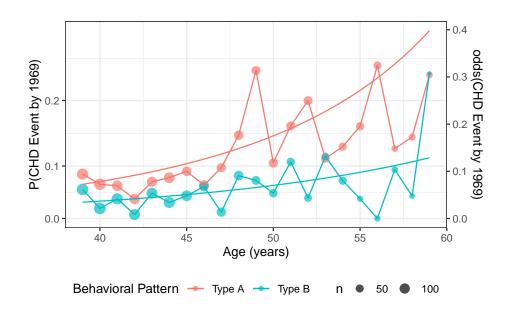


3.6.9.2. odds scale

```
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)
```



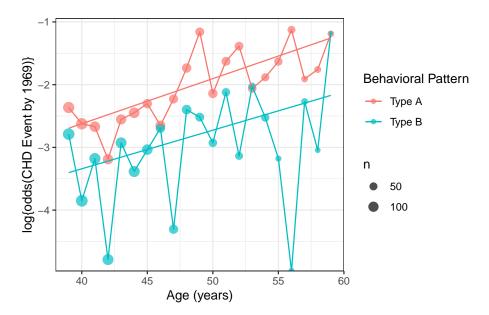
3.6.9.3. log-odds (logit) scale

```
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)
```



3.6.10. 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()
```

Table 3.11.: CHD model (corner-point parametrization)

	Log-				
Parameter	olds	SE	95% CI	\mathbf{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 Table 3.10:

Exercise 3.13. If I give you model 1, how would you get the coefficients of model 2?

3.7. Fitting logistic regression models

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 (c.f., 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.

3.8. Model comparisons for logistic models

3.8.1. 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), ℓ_{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 β 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.

5

Caution

The deviance statistic needs to have a large amount of data for each covariate pattern for the χ^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.

3.8.2. 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; g = 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 χ^2 distribution; by simulation, the degrees of freedom has been found to be approximately g-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]	$2,\!305$	129	135.2

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

```
print(X2)
#> [1] 6.7811383

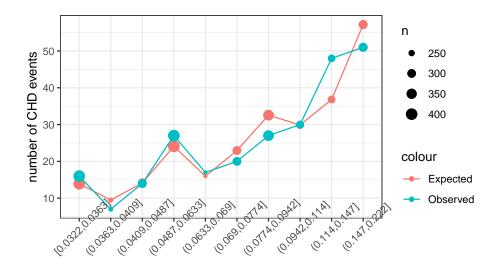
pval1 = pchisq(X2, lower = FALSE, df = nrow(HL_table) - 2)
```

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

3.8.3. 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]

3.9. Residual-based diagnostics

3.9.1. 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()
```

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

3.9.2. (Response) residuals

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

(k indexes the covariate patterns)

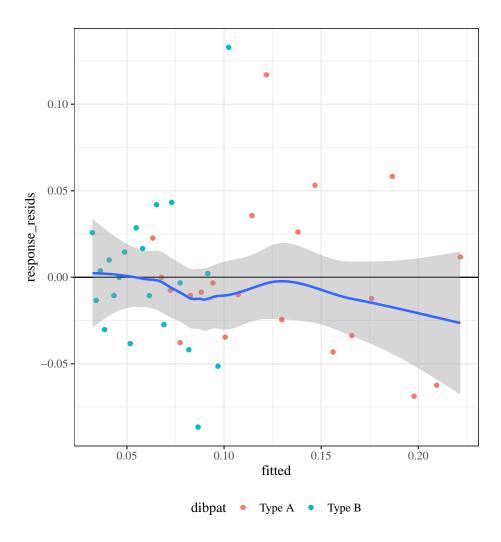
We can graph these residuals e_k against the fitted values $\hat{\pi}(x_k)$:

```
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(
                                                             (1)
   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::lowes; 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 $\pi=0.5$).

3.9.3. 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

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

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



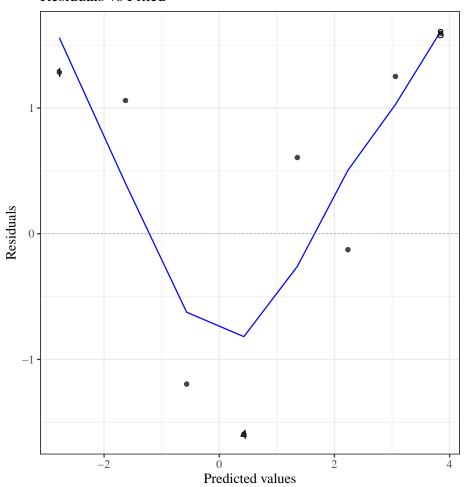
The fan-shape is gone, and these residuals don't show any obvious signs of model fit issues.

3.9.3.1. 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



3.9.3.2. 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.

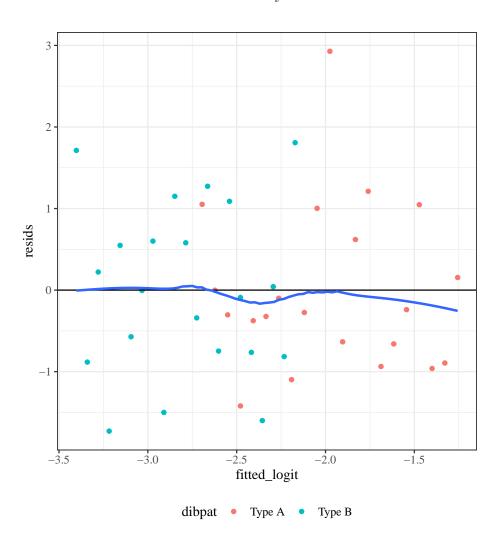
3.9.3.3. Residuals plot by hand (optional section)

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/
```



3.9.4. 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.

3.9.4.1. 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.

3.9.5. 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).

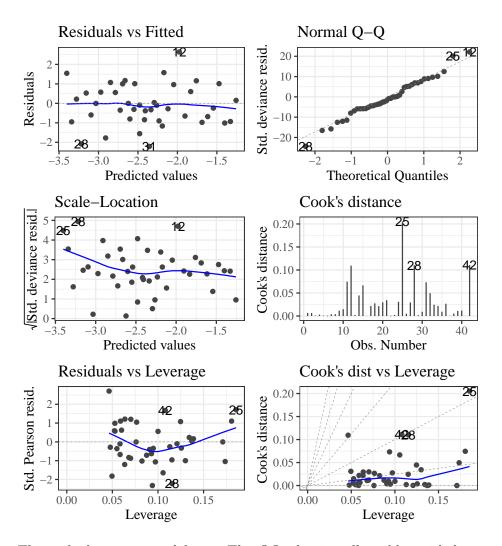
$$d_k = \mathrm{sign}(y_k - n_k \hat{\pi}_k) \left\{ \sqrt{2[\ell_{\mathrm{full}}(x_k) - \ell(\hat{\beta}; x_k)]} \right\}$$

3.9.5.1. Standardized deviance residuals

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

3.9.6. 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.

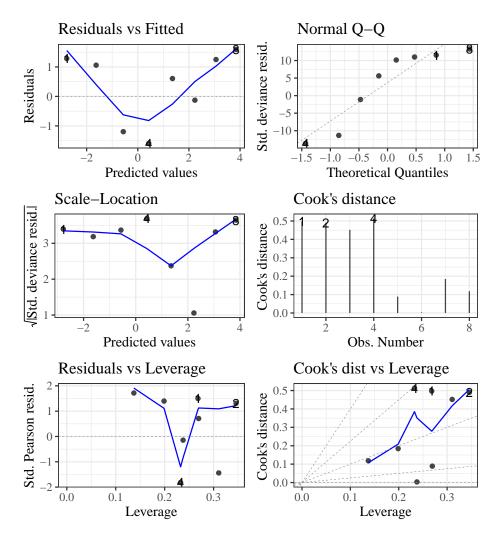
3. Models for Binary Outcomes

3.9.6.1. Beetles

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

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

3. Models for Binary Outcomes



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

3.10. Odds Ratios vs Probability (Risk) Ratios

3.10.0.1. 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
```

3.10.0.2. 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:

3. Models for Binary Outcomes

```
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	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,
```

3. Models for Binary Outcomes

```
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.

4. Models for Count Outcomes

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:

Acknowledgements

```
library(conflicted) # check for conflicting function definitions
# library(printr) # inserts help-file output into markdown output
library(rmarkdown) # Convert R Markdown documents into a variety of formats.
library(pander) # format tables for markdown
library(ggplot2) # graphics
library(ggeasy) # help with graphics
library(ggfortify) # help with graphics
library(dplyr) # manipulate data
library(tibble) # `tibble`s extend `data.frame`s
library(magrittr) # `%>%` and other additional piping tools
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(haven) # import Stata files
library(latex2exp) # use LaTeX in R code (for figures and tables)
library(fs) # filesystem path manipulations
library(survival) # survival analysis
library(survminer) # survival analysis graphics
library(KMsurv) # datasets from Klein and Moeschberger
library(parameters) # format model output tables for
library(webshot2) # convert interactive content to static for pdf
library(forcats) # functions for categorical variables ("factors")
library(stringr) # functions for dealing with strings
library(lubridate) # functions for dealing with dates and times
```

Here are some R settings I use in this document:

```
rm(list = ls()) # delete any data that's already loaded into R
conflicts_prefer(dplyr::filter)
```

Acknowledgements

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

$$\mu = \lambda t$$

 λ 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, λ 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 β 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.

? Tip

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

Therefore, according to this model, differences of δ 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:

$$\begin{cases} \log\left\{\mathbb{E}[Y|\mathbf{X}_{j}=a,\tilde{X}_{-j}=\tilde{x}_{-j},T=t]\right\} \\ -\log\left\{\mathbb{E}[Y|\mathbf{X}_{j}=b,\tilde{X}_{-j}=\tilde{x}_{-j},T=t]\right\} \end{cases} \\ = \begin{cases} \log\left\{t\right\} + \beta_{0} + \beta_{1}x_{1} + \ldots + \beta_{j}(a) + \ldots + \beta_{p}x_{p} \\ -\log\left\{t\right\} + \beta_{0} + \beta_{1}x_{1} + \ldots + \beta_{j}(b) + \ldots + \beta_{p}x_{p} \right\} \\ = \beta_{j}(a-b) \end{cases}$$

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

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

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.

Acknowledgements

Even though we never observe Z, we can estimate the parameters γ_0 - γ_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

$$P(Y=y,Z=z|\ldots)=P(Y=y|Z=z,\ldots)P(Z=z|\ldots)$$

Exercise 4.1. 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 = t)

x, T = t) and P(Y = y | Z = 0, X = x, T = t).

Exercise 4.2. 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).

Acknowledgements

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 ρ 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 μ 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 $Var(Y) = \mu\theta$, and estimates θ 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. ¹ 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.

¹Binary 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(conflicted) # check for conflicting function definitions
# library(printr) # inserts help-file output into markdown output
library(rmarkdown) # Convert R Markdown documents into a variety of formats.
library(pander) # format tables for markdown
library(ggplot2) # graphics
library(ggeasy) # help with graphics
library(ggfortify) # help with graphics
library(dplyr) # manipulate data
library(tibble) # `tibble`s extend `data.frame`s
library(magrittr) # `%>%` and other additional piping tools
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(haven) # import Stata files
library(latex2exp) # use LaTeX in R code (for figures and tables)
library(fs) # filesystem path manipulations
```

```
library(survival) # survival analysis
library(survminer) # survival analysis graphics
library(KMsurv) # datasets from Klein and Moeschberger
library(parameters) # format model output tables for
library(webshot2) # convert interactive content to static for pdf
library(forcats) # functions for categorical variables ("factors")
library(stringr) # functions for dealing with strings
library(lubridate) # functions for dealing with dates and times
```

Here are some R settings I use in this document:

```
rm(list = ls()) # delete any data that's already loaded into R

conflicts_prefer(dplyr::filter)
ggplot2::theme_set(
    ggplot2::theme_bw() +
        # ggplot2::labs(col = "") +
        ggplot2::theme(
        legend.position = "bottom",
        text = ggplot2::element_text(size = 12, family = "serif")))

knitr::opts_chunk$set(message = FALSE)
options('digits' = 4)

panderOptions("big.mark", ",")
pander::panderOptions("table.emphasize.rownames", FALSE)
pander::panderOptions("table.split.table", Inf)
conflicts_prefer(dplyr::filter) # use the `filter()` function from dplyr() by defaul
legend_text_size = 9
```

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:

$$f(t) \stackrel{\text{def}}{=} p(t) \stackrel{\text{def}}{=} p(T=t)$$

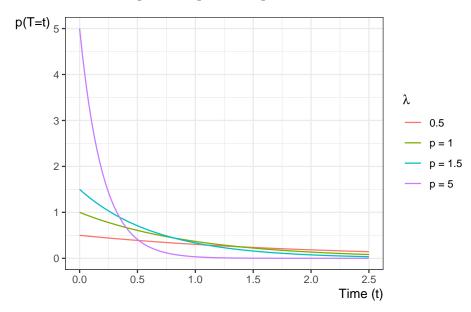
Typically, this density is assumed to be 0 for all t < 0; that is, $f(t) = 0, \forall t < 0$. In other words, the range of T is typically $[0, \infty)$.

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:

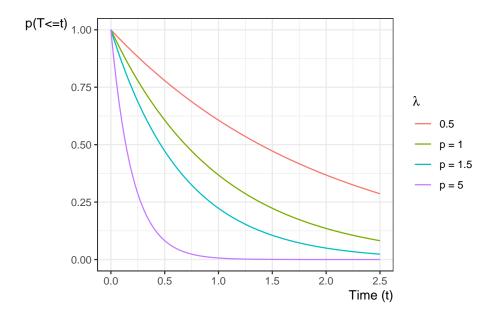
$$S(t) = \mathbb{E}\left[X_t\right]$$

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 $T \geq t$; 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:

$$\begin{split} P(T=t|T\geq t) &= \frac{f(t)}{S(t)} \\ &= \frac{\mathbb{1}_{t\geq 0} \cdot \lambda \mathrm{e}^{-\lambda t}}{\mathrm{e}^{-\lambda t}} \\ &= \mathbb{1}_{t>0} \cdot \lambda \end{split}$$

Figure 5.1 shows some examples of exponential hazard functions:

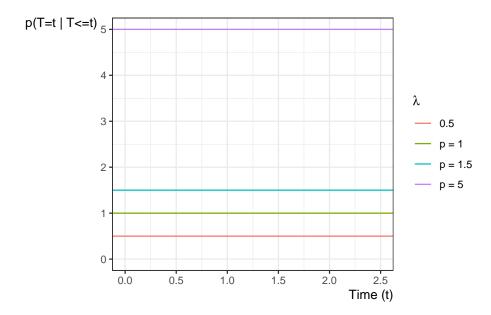


Figure 5.1.: Examples of hazard functions for exponential distributions

We can also view the hazard function as the derivative of the negative of the logarithm of the survival function:

Theorem 5.2.

$$h(t) = \frac{\partial}{\partial t} \left\{ -\log \left\{ S(t) \right\} \right\}$$

Proof.

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

$$= \frac{-S'(t)}{S(t)}$$

$$= -\frac{S'(t)}{S(t)}$$

$$= -\frac{\partial}{\partial t} \log \{S(t)\}$$

$$= \frac{\partial}{\partial t} \{-\log \{S(t)\}\}$$

5.3.5. The Cumulative Hazard Function

Since $h(t) = \frac{\partial}{\partial t} \{-\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:

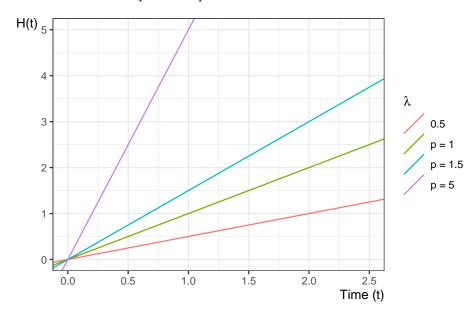
$$H(t) \stackrel{\mathrm{def}}{=} \int_{u=0}^{t} h(u) du$$

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:

$$H(t) = \mathbb{1}_{t > 0} \cdot \lambda t$$

Here are some examples of exponential cumulative hazard functions:



5.3.6. Some Key Mathematical Relationships among Survival Concepts

Diagram:

$$h(t) \xrightarrow{\int_{u=0}^{t} h(u)du} H(t) \xrightarrow{\exp\{-H(t)\}} S(t) \xrightarrow{1-S(t)} F(t)$$

$$h(t) \xleftarrow{\frac{\partial}{\partial t} H(t)} H(t) \xleftarrow{-\log\{S(t)\}} S(t) \xleftarrow{1-F(t)} F(t)$$

Identities:

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

$$= \exp \{-H(t)\}$$

$$S'(t) = -f(t)$$

$$H(t) = -\log \{S(t)\}$$

$$H'(t) = h(t)$$

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

$$= -\frac{\partial}{\partial t} \log \{S(t)\}$$

$$f(t) = h(t) \cdot S(t)$$

Some proofs (others left as exercises):

$$S'(t) = \frac{\partial}{\partial t}(1 - F(t))$$

$$= -F'(t)$$

$$= -f(t)$$

$$\frac{\partial}{\partial t}\log\{S(t)\} = \frac{S'(t)}{S(t)}$$

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

$$= -h(t)$$

$$H(t) \stackrel{\text{def}}{=} \int_{u=0}^{t} h(u)du$$

$$= \int_{0}^{t} -\frac{\partial}{\partial u} \log \{S(u)\} du$$

$$= \left[-\log \{S(u)\} \right]_{u=0}^{u=t}$$

$$= \left[\log \{S(u)\} \right]_{u=t}^{u=0}$$

$$= \log \{S(0)\} - \log \{S(t)\}$$

$$= \log \{1\} - \log \{S(t)\}$$

$$= 0 - \log \{S(t)\}$$

$$= -\log \{S(t)\}$$

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:

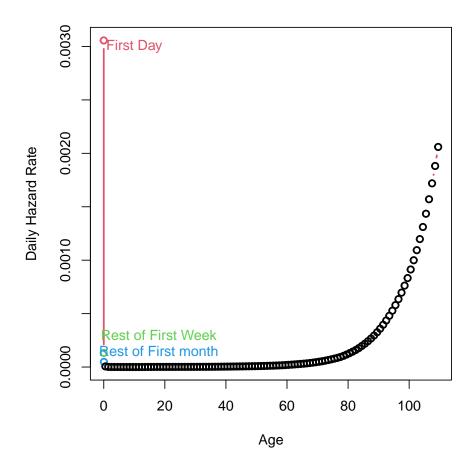


Figure 5.2.: Daily Hazard Rates in 2004 for US Females

Daily hazard rates for US Males and Females in 2004

Exercise: hypothesize why these curves differ where they do?

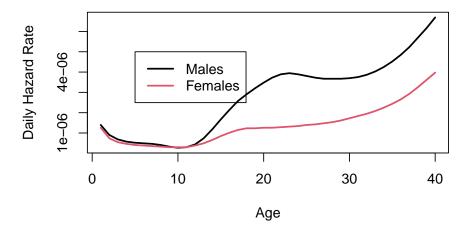


Figure 5.3.: Daily Hazard Rates in 2004 for US Males and Females 1-40 $\,$

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

- θ_T represent the parameters of $p_T(t)$,
- θ_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:

$$\begin{split} \ell'(y,d) &= \frac{\partial}{\partial \theta} \left[\log \left\{ f_T(y)^d \cdot S_T(y)^{1-d} \right\} + \log \left\{ f_C(y)^{1-d} \cdot S_C(y)^d \right\} \right] \\ &= \left(\frac{\partial}{\partial \theta} \log \left\{ f_T(y)^d \cdot S_T(y)^{1-d} \right\} \right) + \left(\frac{\partial}{\partial \theta} \log \left\{ f_C(y)^{1-d} \cdot S_C(y)^d \right\} \right) \end{split}$$

As long as θ_C and θ_T don't share any parameters, then if censoring is non-informative, the partial derivative with respect to θ_T is:

$$\begin{split} \ell_{\theta_T}'(y,d) & \stackrel{\text{def}}{=} \frac{\partial}{\partial \theta_T} \ell(y,d) \\ & = \left(\frac{\partial}{\partial \theta_T} \log \left\{ f_T(y)^d \cdot S_T(y)^{1-d} \right\} \right) + \left(\frac{\partial}{\partial \theta_T} \log \left\{ f_C(y)^{1-d} \cdot S_C(y)^d \right\} \right) \\ & = \left(\frac{\partial}{\partial \theta_T} \log \left\{ f_T(y)^d \cdot S_T(y)^{1-d} \right\} \right) + 0 \\ & = \frac{\partial}{\partial \theta_T} \log \left\{ f_T(y)^d \cdot S_T(y)^{1-d} \right\} \end{split}$$

Thus, the MLE for θ_T won't depend on θ_C , and we can ignore the distribution of C when estimating the parameters of $f_T(t) = p(T = t)$.

Then:

$$\begin{split} \mathcal{L}(y,d) &= f_T(y)^d \cdot S_T(y)^{1-d} \\ &= \left(h_T(y)^d S_T(y)^d \right) \cdot S_T(y)^{1-d} \\ &= h_T(y)^d \cdot S_T(y)^d \cdot S_T(y)^{1-d} \\ &= h_T(y)^d \cdot S_T(y) \\ &= S_T(y) \cdot h_T(y)^d \end{split}$$

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 λ
- The mean survival time is λ^{-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 λ

- 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 λ .

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

$$\log\left\{\lambda\mathrm{e}^{-\lambda t_i}\right\} = \log\left\{\lambda\right\} - \lambda t_i$$

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 $U = \sum u_j$. 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

$$E[-\ell''] = m/\lambda^2$$

$$\operatorname{Var}(\hat{\lambda}) \approx (E[-\ell''])^{-1}$$

$$= \lambda^2/m$$

$$\operatorname{SE}(\hat{\lambda}) = \sqrt{\operatorname{Var}(\hat{\lambda})}$$

$$\approx \lambda/\sqrt{m}$$

 $\hat{\lambda}$ depends on the censoring times of the censored observations, but $\operatorname{Var}(\hat{\lambda})$ 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
                                t2 relapse
                         t1
#>
      <int>
               <int> <int> <int>
                                     <int>
#>
    1
          1
                   1
                         1
                                10
                                          1
    2
           2
                                7
#>
                   2
                         22
                                          1
    3
           3
                   2
                          3
                                32
                                          0
#>
    4
          4
                   2
                         12
                                23
#>
                                          1
    5
          5
                    2
                          8
                                22
#>
    6
          6
                   1
                         17
                                6
                                          1
                   2
#>
    7
          7
                                16
                                          1
#>
    8
          8
                   2
                         11
                                34
                                          0
   9
                          8
                                          0
#>
          9
                   2
                                32
#> 10
                   2
                         12
                                          0
          10
                                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):

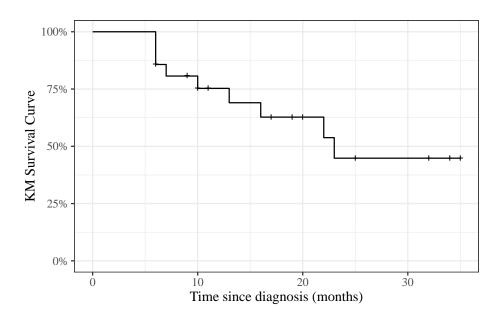


Figure 5.5.: Kaplan-Meier Survival Curve for 6-MP Patients

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		At		Fac-	Cumula	
t2	Rela	ps & enso	or Ec 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 2 .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 3 .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

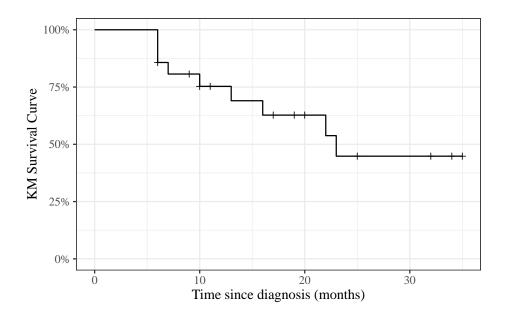
For the 6-MP patients at time 6 months, there are 21 patients at risk. At t = 6 there are 3 relapses and 1 censored observations.

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(
5
          time = t2,
6
          event = (outcome == "relapsed")))
7
   print(drug6mp.v3)
9
   #> # A tibble: 21 x 7
10
           pair remstat
                                    t2 relapse outcome
                              t1
                                                            surv2
11
   #>
          <int> <chr>
                          <int> <int>
                                          <int> <chr>
12
                                                           <Surv>
        1
              1 partial
                              1
                                    10
                                              1 relapsed
                                                              10
13
        2
   #>
              2 complete
                              22
                                     7
                                              1 relapsed
                                                               7
14
   #>
        3
              3 complete
                              3
                                    32
                                              0 censored
                                                              32+
15
       4
                              12
                                              1 relapsed
                                                              23
   #>
              4 complete
                                    23
16
   #>
       5
              5 complete
                              8
                                    22
                                              1 relapsed
                                                              22
17
        6
                              17
                                     6
                                              1 relapsed
                                                               6
   #>
              6 partial
       7
                              2
   #>
              7 complete
                                    16
                                              1 relapsed
                                                              16
        8
              8 complete
                              11
                                    34
                                              0 censored
                                                              34+
20
              9 complete
                              8
                                              0 censored
       9
                                    32
                                                              32+
21
   #> 10
             10 complete
                              12
                                    25
                                              0 censored
                                                              25+
22
   #> # 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 n.event survival std.err lower 95% CI upper 95% CI
#>
#>
             21
                       3
                            0.857
                                    0.0764
                                                   0.720
                                                                 1.000
       7
             17
                       1
                            0.807
                                    0.0869
                                                   0.653
                                                                 0.996
#>
                                    0.0963
#>
      10
             15
                       1
                            0.753
                                                   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
              7
#>
      22
                       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 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
#>
                       1
#>
      16
             11
                            0.627
                                    0.1141
                                                   0.439
                                                                 0.896
              7
      22
                       1
                            0.538
                                    0.1282
                                                                 0.858
#>
                                                   0.337
#>
      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	0.0764		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
#	> 6	21	0	0.857	0.0764		0.720		1.000
#	> 7	17	1	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	10	0	0.627	0.1141		0.439		0.896
#	> 19	9	0	0.627	0.1141		0.439		0.896
#	> 20	8	0	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
#	> 25	5	0	0.448	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
#	> 34	2	0	0.448	0.1346		0.249		0.807
#	> 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)
```

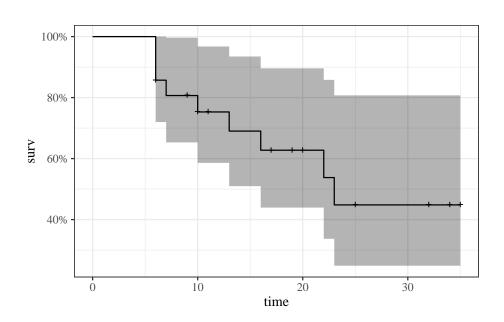


Figure 5.6.: Kaplan-Meier Survival Curve for 6-MP Patients

```
# 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())
```

p	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:

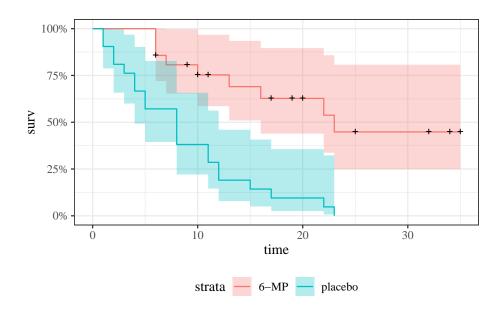
```
library(survival)
drug6mp.v4 =
  drug6mp.v3 |>
  select(pair, remstat, t1, t2, outcome) |>
  # here we are going to change the data from a wide format to long:
  pivot_longer(
    cols = c(t1, t2),
    names_to = "treatment",
    values_to = "exit_time") |>
  mutate(
    treatment = treatment |>
      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)
```

```
#> survdiff(formula = surv ~ treatment, data = drug6mp.v4)
#>
#>
                      N Observed Expected (O-E)^2/E (O-E)^2/V
                     21
                               9
                                      19.3
#> treatment=6-MP
                                                5.46
                                                          16.8
                              21
                                      10.7
                                                9.77
#> treatment=placebo 21
                                                          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)
#> 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
                              21
                                     13.5
                                                4.17
#> treatment=placebo 21
                                                          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(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 O-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
#>
#>
        dp Platelet Recovery Indicator 1-Platelets Returned To Normal,
```

```
#>
             O-Platelets Never Returned to Normal
#>
#>
        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")
```

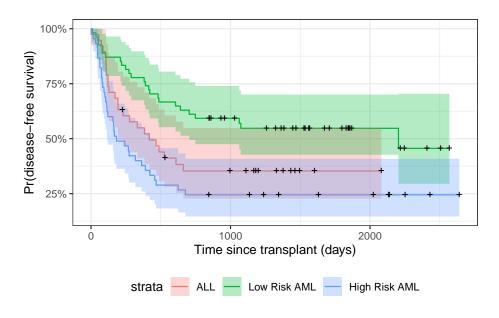


Figure 5.7.: Disease-Free Survival by Disease Group

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

$$\begin{split} \hat{S}(t) &= \prod_{t_i < t} x_i / Y_i \\ S(t) &= \prod_{t_i < t} p_i \end{split}$$

$$S(t) = \prod_{t_i < t} p_i$$

$$\begin{split} \frac{\hat{S}(t)}{S(t)} &= \prod_{t_i < t} \frac{x_i}{p_i Y_i} = \prod_{t_i < t} \frac{\hat{p}_i}{p_i} \\ &= \prod_{t_i < t} \left(1 + \frac{\hat{p}_i - p_i}{p_i} \right) \\ &\approx 1 + \sum_{t_i < t} \frac{\hat{p}_i - p_i}{p_i} \end{split}$$

$$\text{Var}\left(\frac{\hat{S}(t)}{S(t)} \right) \approx \text{Var}\left(1 + \sum_{t_i < t} \frac{\hat{p}_i - p_i}{p_i} \right) \\ &= \sum_{t_i < t} \frac{1}{p_i^2} \frac{p_i (1 - p_i)}{Y_i} \\ &= \sum_{t_i < t} \frac{(1 - p_i)}{p_i Y_i} \approx \sum_{t_i < t} \frac{(1 - x_i / Y_i)}{x_i} \\ &= \sum_{t_i < t} \frac{Y_i - x_i}{x_i Y_i} = \sum_{t_i < t} \frac{d_i}{Y_i (Y_i - d_i)} \end{split}$$

$$\text{Var}\left(\hat{S}(t) \right) \approx \hat{S}(t)^2 \sum_{t_i < t} \frac{d_i}{Y_i (Y_i - d_i)} \end{split}$$

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:

```
survdiff(surv ~ group, data = bmt)
#> Call:
#> survdiff(formula = surv ~ group, data = bmt)
#>

N Observed Expected (O-E)^2/E (O-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 free	dom, p= 0	.001	

5.9.5. Cumulative Hazard

$$\begin{split} h(t) &\stackrel{\text{def}}{=} P(T=t|T \geq t) \\ &= \frac{p(T=t)}{P(T \geq t)} \\ &= -\frac{\partial}{\partial t} \log \left\{ S(t) \right\} \end{split}$$

The cumulative hazard (or integrated hazard) function is

$$H(t) \stackrel{\text{def}}{=} \int_0^t h(t)dt$$

Since $h(t) = -\frac{\partial}{\partial t} \mathrm{log} \left\{ S(t) \right\}$ as shown above, we have:

$$H(t) = -\mathrm{log}\left\{S\right\}(t)$$

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:

5. Introduction to Survival Analysis

$$\begin{split} \hat{\text{Var}}\left(\hat{H}_{NA}(t)\right) &= \sum_{t_i < t} \frac{(d_i/Y_i)(1 - d_i/Y_i)}{Y_i} \\ &\approx \sum_{t_i < t} \frac{d_i}{Y_i^2} \end{split}$$

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")
```

5. Introduction to Survival Analysis

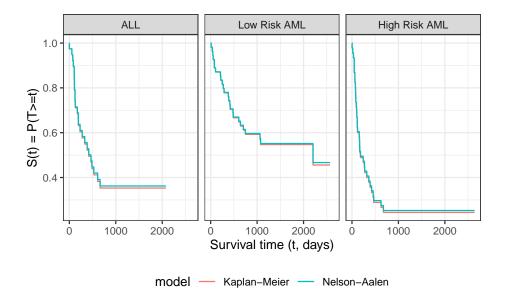


Figure 5.9.: Kaplan-Meier and Nelson-Aalen Survival Function Estimates, stratified by disease group

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(conflicted) # check for conflicting function definitions
# library(printr) # inserts help-file output into markdown output
library(rmarkdown) # Convert R Markdown documents into a variety of formats.
library(pander) # format tables for markdown
library(ggplot2) # graphics
library(ggeasy) # help with graphics
library(ggfortify) # help with graphics
library(dplyr) # manipulate data
library(tibble) # `tibble`s extend `data.frame`s
library(magrittr) # `%>%` and other additional piping tools
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(haven) # import Stata files
```

```
library(latex2exp) # use LaTeX in R code (for figures and tables)
library(fs) # filesystem path manipulations
library(survival) # survival analysis
library(survminer) # survival analysis graphics
library(KMsurv) # datasets from Klein and Moeschberger
library(parameters) # format model output tables for
library(webshot2) # convert interactive content to static for pdf
library(forcats) # functions for categorical variables ("factors")
library(stringr) # functions for dealing with strings
library(lubridate) # functions for dealing with dates and times
```

Here are some R settings I use in this document:

```
rm(list = ls()) # delete any data that's already loaded into R

conflicts_prefer(dplyr::filter)
ggplot2::theme_set(
    ggplot2::theme_bw() +
        # ggplot2::labs(col = "") +
        ggplot2::theme(
        legend.position = "bottom",
        text = ggplot2::element_text(size = 12, family = "serif")))

knitr::opts_chunk$set(message = FALSE)
options('digits' = 4)

panderOptions("big.mark", ",")
pander::panderOptions("table.emphasize.rownames", FALSE)
pander::panderOptions("table.split.table", Inf)
conflicts_prefer(dplyr::filter) # use the `filter()` function from dplyr() by defaul legend_text_size = 9
```

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:

$$\begin{split} \frac{h(t|x_1)}{h(t|x_2)} &= \frac{\theta(x_1)}{\theta(x_2)} \\ &= \frac{\exp\left\{\eta(x_1)\right\}}{\exp\left\{\eta(x_2)\right\}} \\ &= \exp\left\{\eta(x_1) - \eta(x_2)\right\} \\ &= \exp\left\{x_1'\beta - x_2'\beta\right\} \\ &= \exp\left\{(x_1 - x_2)'\beta\right\} \end{split}$$

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 β_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.

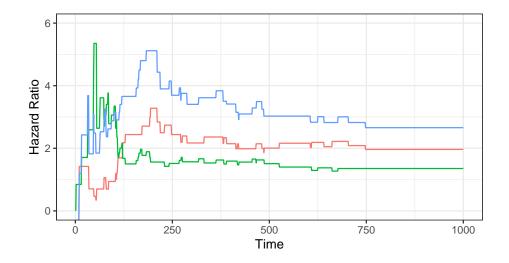
```
library(KMsurv)
library(survival)
data(bmt)

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(
```

```
library(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)
```



 $\hbox{\bf Comparison } \ \hbox{\bf ---} \ \ \hbox{\bf ALL/Low Risk AML} \ \hbox{\bf ---} \ \ \hbox{\bf High Risk AML/ALL} \ \hbox{\bf ---} \ \ \hbox{\bf High Risk AML/Low Risk}$

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))
```

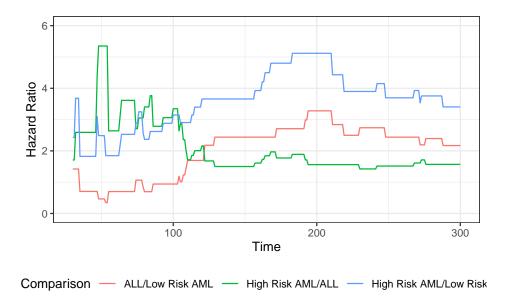


Figure 6.2.: Hazard Ratios by Disease Group (30-300 Days)

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)
```

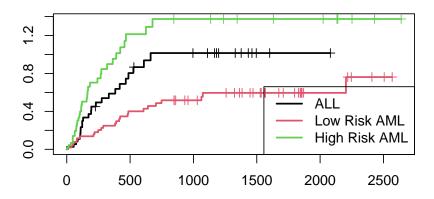


Figure 6.3.: Disease-Free Cumulative Hazard by Disease Group

```
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)
```

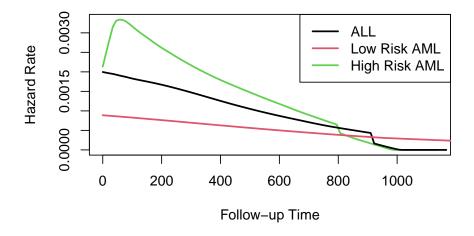


Figure 6.4.: Smoothed Hazard Rate Estimates by Disease Group

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 β 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|)
#> groupLow Risk AML -0.574 0.563
                                          0.287 - 2.00
                                                         0.046 *
#> groupHigh Risk AML 0.383
                                          0.267 1.43
                                                         0.152
                                1.467
#> Signif. codes: 0 '***' 0.001 '**' 0.05 '.' 0.1 ' ' 1
#>
                      exp(coef) exp(-coef) lower .95 upper .95
                          0.563
#> groupLow Risk AML
                                    1.776
                                               0.321
```

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

#>

#>

#>

#>

#>

#>

#>

172

192

194

230

276

332

383

27

26

25

23

22

21

20

1

1

1

1

1

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
                        38
                                24
                                      418
                                               194
                                                         NA
#> group=Low Risk AML
                        54
                                25
                                     2204
                                               704
                                                         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
                             0.947
                                    0.0362
                                                   0.879
                                                                 1.000
#>
                       1
      74
#>
             36
                       1
                            0.921
                                    0.0437
                                                   0.839
                                                                 1.000
                                    0.0498
#>
      86
             35
                       1
                            0.895
                                                   0.802
                                                                 0.998
#>
     104
             34
                       1
                            0.868
                                    0.0548
                                                   0.767
                                                                 0.983
#>
     107
             33
                       1
                            0.842
                                    0.0592
                                                   0.734
                                                                 0.966
     109
             32
                                    0.0629
                                                   0.701
#>
                       1
                            0.816
                                                                 0.949
#>
     110
             31
                       1
                             0.789
                                    0.0661
                                                   0.670
                                                                 0.930
#>
     122
             30
                       2
                            0.737
                                    0.0714
                                                   0.609
                                                                 0.891
#>
     129
             28
                       1
                            0.711
                                    0.0736
                                                   0.580
                                                                 0.870
```

0.684

0.658

0.632

0.604

0.577

0.549

0.0754

0.0770

0.0783

0.0795

0.0805

0.0812

0.522 0.0817

0.551

0.523

0.495

0.467

0.439

0.411

0.384

0.849

0.827

0.805

0.782

0.758

0.734

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
#>							
#>			grou	p=Low Rish	x AML		
#>	time	n.risk	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	0.998
#>	79	50	1	0.907	0.0394	0.833	0.988
#>	80	49	1	0.889	0.0428	0.809	0.977
#>	105	48	1	0.870	0.0457	0.785	0.965
#>	211	47	1	0.852	0.0483	0.762	0.952
#>	219	46	1	0.833	0.0507	0.740	0.939
#>	248	45	1	0.815	0.0529	0.718	0.925
#>	272	44	1	0.796	0.0548	0.696	0.911
#>	288	43	1	0.778	0.0566	0.674	0.897
#>	381	42	1	0.759	0.0582	0.653	0.882
#>	390	41	1	0.741	0.0596	0.633	0.867
#>	414	40	1	0.722	0.0610	0.612	0.852
#>	421	39	1	0.704	0.0621	0.592	0.837
#>	481	38	1	0.685	0.0632	0.572	0.821
#>	486	37	1	0.667	0.0642	0.552	0.805
#>	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	
	#>								
	#>	0 1 0 1							
	#>	time	n.risk	${\tt n.event}$	survival	$\operatorname{std.err}$	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	
	#>	390	17	1	0.356	0.0714	0.240	0.527	
	#>	422	16	1	0.333	0.0703	0.221	0.504	

survfit(bmt.cox)

#>

53

127

```
#>
     456
             15
                             0.311
                                    0.0690
                                                   0.201
                                                                  0.481
     467
              14
                             0.289
                                    0.0676
                                                    0.183
                                                                  0.457
#>
                       1
#>
     625
              13
                       1
                             0.267
                                    0.0659
                                                    0.164
                                                                  0.433
#>
     677
              12
                             0.244 0.0641
                                                   0.146
                                                                  0.409
```

```
#> Call: survfit(formula = bmt.cox)
          n events median 0.95LCL 0.95UCL
#>
#> [1,] 137
                83
                       422
                               268
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
                                     NA
#> 2 137
                                     NA
             83
                    NA
                            625
                    268
#> 3 137
             83
                            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
                       1
                             0.993
                                        0.996
                                                  0.989
       2
                       1
            136
                             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
                             0.955
                                        0.975
#>
      35
            132
                       1
                                                  0.935
      47
            131
                       2
#>
                             0.941
                                        0.966
                                                  0.914
                       2
#>
      48
            129
                             0.926
                                        0.957
                                                  0.893
```

0.953

0.882

0.918

#>	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	
#>	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 $\theta_1, \theta_2, \theta_3$ and let the sum of the risk parameters of the remaining 17 individuals be θ_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(conflicted) # check for conflicting function definitions
# library(printr) # inserts help-file output into markdown output
library(rmarkdown) # Convert R Markdown documents into a variety of formats.
library(pander) # format tables for markdown
library(ggplot2) # graphics
library(ggeasy) # help with graphics
library(ggfortify) # help with graphics
library(dplyr) # manipulate data
library(tibble) # `tibble`s extend `data.frame`s
library(magrittr) # `%>%` and other additional piping tools
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(haven) # import Stata files
```

```
library(latex2exp) # use LaTeX in R code (for figures and tables)
library(fs) # filesystem path manipulations
library(survival) # survival analysis
library(survminer) # survival analysis graphics
library(KMsurv) # datasets from Klein and Moeschberger
library(parameters) # format model output tables for
library(webshot2) # convert interactive content to static for pdf
library(forcats) # functions for categorical variables ("factors")
library(stringr) # functions for dealing with strings
library(lubridate) # functions for dealing with dates and times
```

Here are some R settings I use in this document:

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
#>
      gtype
               dtype
                             time delta score wtime
                                                      surv
#>
     <chr>
               <fct>
                            <int> <chr> <int> <int> <Surv>
   1 Allogenic Non-Hodgkins 28 dead
                                                 24
                                                       28
                                           90
                                                 7
  2 Allogenic Non-Hodgkins
                              32 dead
                                           30
                                                       32
  3 Allogenic Non-Hodgkins
                             49 dead
                                           40
                                                 8
                                                       49
#> 4 Allogenic Non-Hodgkins
                              84 dead
                                           60
                                                 10
                                                      84
#> 5 Allogenic Non-Hodgkins
                              357 dead
                                           70
                                                 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 2114 alive 80 27 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
#> dtypeHodgkins
                            2.7603 15.8050 0.9474 2.91
                                                         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
#> Signif. codes: 0 '***' 0.001 '**' 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
                                      1.0507 0.9288
                              0.9517
                                                         0.975
#> wtime
                             0.9836
                                      1.0167
                                               0.9641
                                                         1.003
#> gtypeAutologous:dtypeHodgkins 0.0934
                                      10.7074 0.0123
                                                         0.711
#>
```

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)")
```

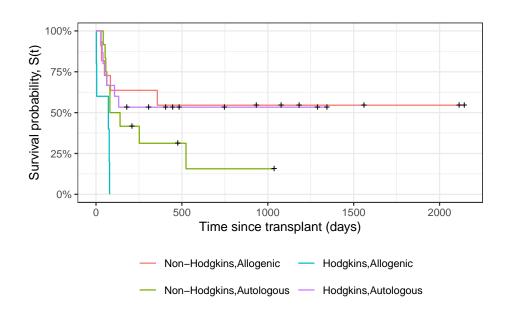


Figure 7.1.: Kaplan-Meier Survival Curves for HOD/NHL and Allo/Auto Grafts

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)))
```

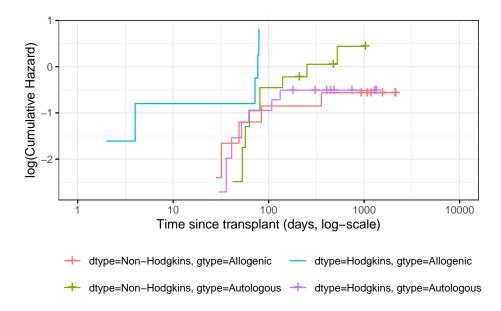


Figure 7.3.: Complementary log-log survival curves - Nelson-Aalen estimates

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) = 0.1266 years, or 1/40 of the mean lifetime.

- The upper end is at the 0.975 point which is qexp(.975, rate = 1/5) = 18.4444 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 θ_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 p

#> gtype 0.5400 1 0.462

#> dtype 1.8012 1 0.180

#> score 3.8805 1 0.049

#> wtime 0.0173 1 0.895

#> gtype:dtype 4.0474 1 0.044

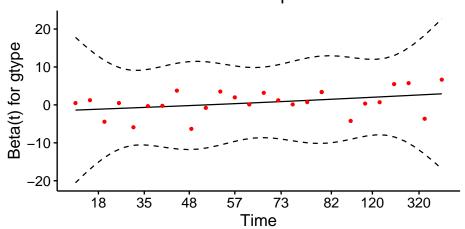
#> GLOBAL 13.7573 5 0.017
```

7.3.6.1. gtype

```
ggcoxzph(hodg.zph, var = "gtype")
```

Global Schoenfeld Test p: 0.01723

Schoenfeld Individual Test p: 0.4624

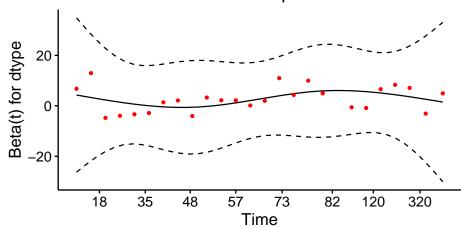


7.3.6.2. dtype

ggcoxzph(hodg.zph, var = "dtype")

Global Schoenfeld Test p: 0.01723

Schoenfeld Individual Test p: 0.1796

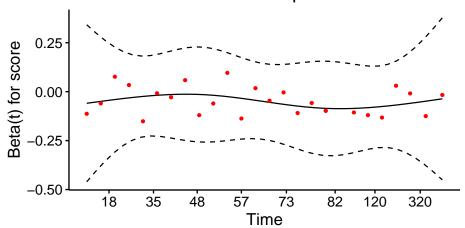


7.3.6.3. score

ggcoxzph(hodg.zph, var = "score")

Global Schoenfeld Test p: 0.01723

Schoenfeld Individual Test p: 0.0489

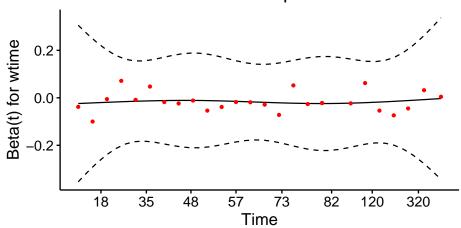


7.3.6.4. wtime

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^{-x}

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 δ_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 = ""))
```

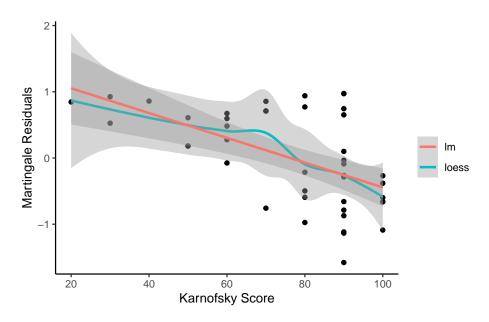


Figure 7.7.: Martingale Residuals vs. Karnofsky Score

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")
#> # A tibble: 4 x 4
#>
       Df
          AIC LRT `Pr(>Chi)`
#>
    <dbl> <dbl> <dbl>
                          <dbl>
#> 1
       NA 152. NA
                     NA
#> 2
        1 168. 17.2
                      0.0000330
#> 3
        1 154. 3.28 0.0702
#> 4
       1 156. 5.44 0.0197
```

```
hodg.cox2 |> drop1(test="Chisq")

#> # A tibble: 4 x 4

#> Df AIC LRT `Pr(>Chi)`

#> <dbl> <dbl> <dbl> <dbl>
#> 1 NA 149. NA NA

#> 2 1 169. 21.6 0.00000335
```

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")
```

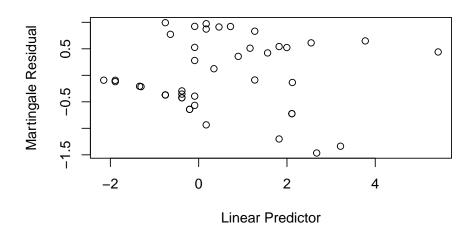


Figure 7.9.: Martingale Residuals vs. Linear Predictor

The smallest three martingale residuals in order are observations 1, 29, and 18.

plot(hodg.preds,hodg.dev,xlab="Linear Predictor",ylab="Deviance Residual")

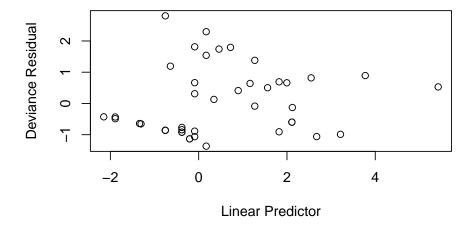


Figure 7.10.: Deviance Residuals vs. Linear Predictor

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")
```

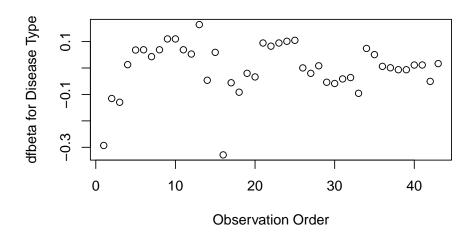


Figure 7.12.: dfbeta Values by Observation Order for Disease Type

The smallest two dfbeta values for disease type are observations 1 and 16.

7.6.3.3. Karnofsky score

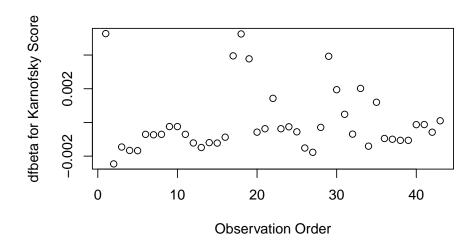


Figure 7.13.: dfbeta Values by Observation Order for Karnofsky Score

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")
```

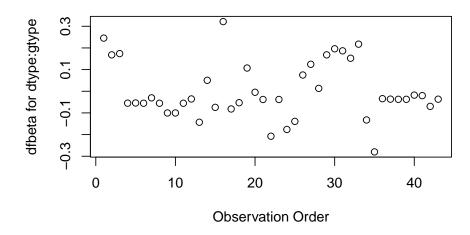


Figure 7.15.: dfbeta Values by Observation Order for dtype:gtype

The two largest values are observations 1 and 16. The smallest value is observation 35.

Table 7.1.: 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.
#>
       2.0 41.2
                   62.5
                             97.6 83.2
                                            524.0
with(hodg,summary(wtime))
     Min. 1st Qu. Median
                             Mean 3rd Qu.
                                             Max.
       5.0 16.0
                   24.0
                             37.7 55.5
                                            171.0
with(hodg,summary(score))
     Min. 1st Qu. Median
#>
                             Mean 3rd Qu.
                                             Max.
     20.0 60.0
                     80.0
                             76.3
                                     90.0
                                            100.0
hodg.cox2
#> Call:
#> coxph(formula = Surv(time, event = delta == "dead") ~ gtype *
       dtype + score + wt2, data = hodg2)
#>
#>
#>
                                 coef exp(coef) se(coef) z
                                                    0.59 1 0.263
#> gtypeAutologous
                                 0.67
                                           1.94
#> 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 - 20.050
#> 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"
      ))
#> # A tibble: 5 x 7
     gtype
                dtype
                              time delta score wtime comment
#>
     <chr>
                <fct>
                              <int> <chr> <int> <int> <chr>
#> 1 Allogenic Non-Hodgkins
                                 28 dead
                                             90
                                                   24 early death, good score, low ~
#> 2 Allogenic Hodgkins
                                 77 dead
                                             60
                                                  102 high risk grp, long wait, poo~
#> 3 Allogenic Hodgkins
                                                   71 high risk grp, short wait, po~
                                 79 dead
                                             70
#> 4 Autologous Non-Hodgkins
                                 53 dead
                                             90
                                                   17 early death, good score, med ~
#> 5 Autologous Hodgkins
                                                   73 early death, good score, med ~
                                 30 dead
                                             90
```

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 7.2.: 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
                   #> ---
#> Signif. codes: 0 '***' 0.001 '**' 0.05 '.' 0.1 ' ' 1
#>
#>
       exp(coef) exp(-coef) lower .95 upper .95
#> rxnew
           0.222
                     4.498
                             0.090 0.549
#> sexmale
           1.370
                      0.730
                               0.562
                                       3.338
#> 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
```

7.7.2.1. Test the proportional hazards assumption

```
cox.zph(anderson.cox1)

#> chisq df p

#> rx 0.036 1 0.85

#> 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"
)
```

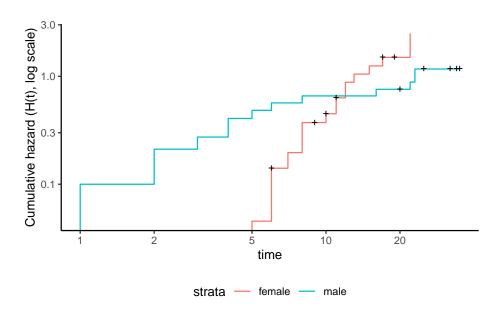


Figure 7.16.: Cumulative hazard (cloglog scale) for anderson data

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|)
#> rxnew -0.998
                     0.369
                              0.474 - 2.11
                                             0.035 *
                     4.279
                              0.344 4.22 2.4e-05 ***
#> logwbc 1.454
#> ---
#> Signif. codes: 0 '***' 0.001 '**' 0.05 '.' 0.1 ' ' 1
#>
          exp(coef) exp(-coef) lower .95 upper .95
#> rxnew
              0.369
                         2.713
                                   0.146
                                             0.932
              4.279
                         0.234
#> logwbc
                                   2.180
                                             8.398
```

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|)
#> rxnew -1.978 0.138 0.739 -2.68 0.0075 **
                            0.536 3.25
#> logwbc 1.743
                   5.713
                                        0.0011 **
#> Signif. codes: 0 '***' 0.001 '**' 0.05 '.' 0.1 ' ' 1
#>
         exp(coef) exp(-coef) lower .95 upper .95
#> rxnew
             0.138
                       7.227
                                0.0325
             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
#>
#>
         coef exp(coef) se(coef) z Pr(>|z|)
#> 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
#> logwbc
            3.341
                      0.299
                              1.245
                                        8.96
#>
#> Concordance= 0.692 (se = 0.085 )
#> Likelihood ratio test= 6.65 on 2 df, p=0.04
\#> Wald test = 6.36 \text{ 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 different?

```
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
#> logwbc
                         1.206
                                    3.341
                                          0.503 2.40
                                                           0.017 *
#> strata(sex)male:rxnew -1.667
                                          0.930 -1.79
                                   0.189
                                                           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
#> rxnew
                             0.733
                                       1.365
                                                0.2427
                                                            2.21
#> 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
```

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 non-proportionality 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 =
   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
               #> logwbc
               1.0637
                         2.8971 0.4726 2.25
                                              0.024 *
               -2.8052 0.0605 2.0323 -1.38 0.167
#> sexmale
#> rxnew:sexmale -2.1782
                       0.1132 0.9109 -2.39 0.017 *
#> 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
#> rxnew
                 0.6874
                            1.455
                                  0.23185
                                              2.038
#> logwbc
                 2.8971
                            0.345 1.14730
                                              7.315
                          16.531 0.00113
#> sexmale
                 0.0605
                                              3.248
#> rxnew:sexmale 0.1132
                           8.830 0.01899
                                             0.675
                                           11.766
#> logwbc:sexmale 3.4223
                           0.292 0.99539
#> Concordance= 0.861 (se = 0.036 )
#> Likelihood ratio test= 57 on 5 df, p=5e-11
\#> Wald test = 35.6 on 5 df, p=1e-06
\# Score (logrank) test = 57.1 on 5 df, p=5e-11
```

```
cox.zph(anderson.coxph.intxn)
#>
              chisq df
#> rx
              0.136
                    1 0.71
#> logwbc
                    1 0.20
              1.652
#> 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
```

7.8. Time-varying covariates

(adapted from Klein, Moeschberger, et al. (2003), §9.2)

7.8.1. Motivating example: back to the leukemia dataset

```
# load the data:
data(bmt, package = 'KMsurv')
bmt |> as_tibble() |> print(n = 5)
#> # A tibble: 137 x 22
    group
            t1
                  t2
                       d1
                             d2
                                  d3
                                             da
                                                   tc
                                        ta
                                                        dc
                                                              tp
                                                                   dp
                                                                         z1
    #> 1
        1
          2081 2081
                        0
                              0
                                   0
                                        67
                                              1
                                                  121
                                                         1
                                                              13
                                                                    1
                                                                         26
#> 2
        1
          1602
               1602
                        0
                              0
                                   0
                                     1602
                                              0
                                                  139
                                                         1
                                                              18
                                                                    1
                                                                         21
#> 3
          1496
               1496
                              0
                                   0
                                      1496
                                              0
                                                  307
                                                         1
                                                              12
                                                                    1
                                                                         26
        1
                        0
#> 4
        1 1462
               1462
                              0
                                   0
                                       70
                                              1
                                                  95
                                                         1
                                                              13
                                                                         17
#> 5
        1 1433
               1433
                              0
                                     1433
                                              0
                                                  236
                                                         1
                                                              12
                                                                         32
#> # 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
#> group id `patient age` `donor age` `patient sex` `donor sex`
```

#>		<fct></fct>	<int></int>	<int></int>	<int></int>	<chr></chr>	<chr></chr>
#>	1	ALL	1	26	33	Male	Female
#>	2	ALL	2	21	37	Male	Male
#>	3	ALL	3	26	35	Male	Male
#>	4	ALL	4	17	21	Female	Male
#>	5	ALL	5	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
#\	# -	107 ,	mara ratta				

#> # i 127 more rows

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

^{#&}gt; # i 6 more variables: `Patient CMV Status` <chr>, `Donor CMV Status` <chr>,
#> # `Waiting Time to Transplant` <int>, FAB <fct>, hospital <fct>, MTX <lgl>

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)
#> # A tibble: 1 x 12
     id
         t1
                 t2
                     d2
                         d3
                                 da
                             ta
                                     tc
                                         dc
                                             tp
                                                 dp
   #> 1 1 2081 0 2081 0 0
                             67
                               1 121 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)
#> # A tibble: 4 x 7
        id tstart tstop agvhd cgvhd precovery status
            <dbl> <int> <int> <int>
                                           <int>
#> 1
         1
                 0
                       13
                              0
                                     0
                                                0
                                                        0
#> 2
         1
                13
                       67
                              0
                                     0
                                                1
                                                        0
         1
                67
                     121
                              1
                                     0
                                                1
                                                        0
#> 3
                    2081
                                     1
                                                        0
#> 4
         1
               121
                              1
```

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
                          #> 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`
                          #> 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 '**' 0.05 '.' 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`
                              0.919
                                        1.088
                                                0.866
                                                          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
\#> Wald test = 33 on 6 df, p=1e-05
#> Score (logrank) test = 35.8 on 6 df, p=3e-06
drop1(bmt_coxph_TF, test = "Chisq")
#> # A tibble: 4 x 4
      Df AIC LRT `Pr(>Chi)`
    <dbl> <dbl> <dbl> <dbl>
#>
#> 1 NA 726. NA
                    NA
#> 2
      2 734. 12.5 0.00192
#> 3
      1 733. 9.22 0.00240
#> 4 1 733. 9.51 0.00204
```

```
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
#> # A tibble: 1 x 13
           dp tc
                              da FAB
      tp
                                       surv
                                              t1
                                                   d1
                                                        t2
                     dc
                          ta
   21 1 220 1
                        418 0 Other
                                        418
                                            418
                                                   1
                                                       418
bmt2 |> dplyr::filter(id == 15) |> dplyr::select(id, agvhd, cgvhd, precovery, surv)
#> # A tibble: 3 x 5
#>
      id agvhd cgvhd precovery
                               surv
   <int> <int> <int>
                     <int>
                              <Surv>
                         0 ( 0, 21+]
#> 1
      15
            0
                 0
                         1 (21,220+]
#> 2
      15
            0
                 0
#> 3
      15
                         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 **
#> groupHigh Risk AML
                              -0.380481 0.683533
                                                   0.374867 - 1.01
                                                                    0.3101
#> `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 **
#> agvhd
                              0.150565 1.162491 0.306848 0.49
                                                                    0.6237
#> cgvhd
                              -0.116136  0.890354  0.289046  -0.40
                                                                    0.6878
                              -0.941123 0.390190 0.347861 -2.71
                                                                    0.0068 **
#> precovery
#> `patient age`: `donor age`     0.002895     1.002899     0.000944     3.07
                                                                    0.0022 **
#> Signif. codes: 0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
#>
                              exp(coef) exp(-coef) lower .95 upper .95
#>
#> groupLow Risk AML
                                  0.354
                                             2.825
                                                     0.175
                                                                 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
                                                                 0.983
                                             1.079
                                                     0.873
#> FABGrade 4 Or 5 (AML only)
                                  2.238
                                             0.447
                                                     1.282
                                                                 3.907
#> agvhd
                                  1.162
                                             0.860
                                                     0.637
                                                                 2.121
#> cgvhd
                                  0.890
                                                      0.505
                                                                 1.569
                                             1.123
#> 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 on 9 df,
                                           p=4e-07
```

Platelet recovery is highly significant.

Neither acute GVHD (agvhd) nor chronic GVHD (cgvhd) has a statisti-

cally 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 **
#> groupHigh Risk AML
                             -0.417049 0.658988 0.365348 -1.14
                                                                  0.2537
#> `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 **
#> cgvhd
                             -0.095393 0.909015 0.285979 -0.33
                                                                  0.7387
#> 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 '**' 0.05 '.' 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
                                                     0.322
                                                               1.349
                                 0.659
                                            1.517
#> `patient age`
                                 0.932
                                            1.073
                                                    0.869
                                                               0.999
#> `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 \text{ 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 **
#> groupHigh Risk AML
                            -0.381356 0.682935 0.374568 -1.02
                                                                 0.3086
#> `patient age`
                            -0.073189 0.929426 0.035890 -2.04
                                                                 0.0414 *
#> `donor age`
                            -0.076753 0.926118 0.030121 -2.55
                                                                 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
#> precovery
                            -0.946697 0.388021 0.347265 -2.73
                                                                 0.0064 **
#> `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
#> groupLow Risk AML
                                0.361
                                           2.772 0.180
                                                              0.724
#> groupHigh Risk AML
                                0.683
                                           1.464
                                                   0.328
                                                              1.423
                                0.929
#> `patient age`
                                          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`
                                                            1.005
                               1.003
                                           0.997
                                                   1.001
#> 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|)
#> groupLow Risk AML
                            -1.032520 0.356108 0.353202 -2.92
                                                                 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 **
                            -0.983505 0.373998 0.337997 -2.91
                                                                 0.0036 **
#> precovery
#> `patient age`: `donor age` 0.002872 1.002876 0.000936 3.07
                                                                 0.0021 **
#> ---
#> 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`
                                           1.079
                                0.927
                                                   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
```

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 7.3.: 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
                1.1778
                       0.0478 3.43 0.00061 ***
#> num
      0.1637
#> size -0.0411
                #> Signif. codes: 0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
#>
#>
      exp(coef) exp(-coef) lower .95 upper .95
         0.663
                   1.509
                            0.448
                                     0.98
#> tx
          1.178
                   0.849
                            1.073
#> num
                                     1.29
#> size
          0.960
                   1.042
                            0.836
                                     1.10
#>
#> Concordance= 0.624 (se = 0.032 )
#> Likelihood ratio test= 14.7 on 3 df,
                                    p=0.002
#> Wald test
                    = 15.9 \text{ on } 3 \text{ 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
                                     0.0584 2.80
#> num
                           0.0478
                                                  0.0051 **
#> size -0.0411 0.9598
                          0.0703
                                     0.0742 - 0.55
                                                    0.5799
#> Signif. codes: 0 '***' 0.001 '**' 0.05 '.' 0.1 ' ' 1
#>
       exp(coef) exp(-coef) lower .95 upper .95
           0.663
                      1.509
                                0.407
                                           1.08
#> tx
           1.178
#> num
                      0.849
                                1.050
                                           1.32
#> size
           0.960
                      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)
#> [,1] [,2] [,3]
```

```
#> [1,] 0.0400 -0.0014 0.0000
#> [2,] -0.0014 0.0023 0.0007
#> [3,] 0.0000 0.0007 0.0049
round(bladder.cox2$var, 4)
#> [,1] [,2] [,3]
#> [1,] 0.0619 -0.0026 -0.0004
#> [2,] -0.0026 0.0034 0.0013
#> [3,] -0.0004 0.0013 0.0055
```

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|)
#> tx -0.4117 0.6625 0.2003
                                  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
```

```
#> num
          1.185
                     0.844
                               1.061
                                          1.32
#>
#> Concordance= 0.623 (se = 0.031 )
#> Likelihood ratio test= 14.3 on 2 df,
                                          p=8e-04
                       = 10.2 on 2 df,
#> Wald test
                                          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).

8. Parametric survival models

Configuring R

Functions from these packages will be used throughout this document:

```
library(conflicted) # check for conflicting function definitions
# library(printr) # inserts help-file output into markdown output
library(rmarkdown) # Convert R Markdown documents into a variety of formats.
library(pander) # format tables for markdown
library(ggplot2) # graphics
library(ggeasy) # help with graphics
library(ggfortify) # help with graphics
library(dplyr) # manipulate data
library(tibble) # `tibble`s extend `data.frame`s
library(magrittr) # `%>%` and other additional piping tools
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(haven) # import Stata files
```

8. Parametric survival models

```
library(latex2exp) # use LaTeX in R code (for figures and tables)
library(fs) # filesystem path manipulations
library(survival) # survival analysis
library(survminer) # survival analysis graphics
library(KMsurv) # datasets from Klein and Moeschberger
library(parameters) # format model output tables for
library(webshot2) # convert interactive content to static for pdf
library(forcats) # functions for categorical variables ("factors")
library(stringr) # functions for dealing with strings
library(lubridate) # functions for dealing with dates and times
```

Here are some R settings I use in this document:

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:

$$\begin{split} f(t) &= \lambda p (\lambda t)^{p-1} e^{-(\lambda t)^p} \\ F(t) &= 1 - e^{-(\lambda t)^p} \\ S(t) &= e^{-(\lambda t)^p} \\ h(t) &= \lambda p (\lambda t)^{p-1} \\ H(t) &= (\lambda t)^p \\ \log \left\{ H(t) \right\} &= p \log \left\{ \lambda t \right\} = p \log \left\{ \lambda \right\} + p \log \left\{ t \right\} \\ \mathrm{E}(T) &= \lambda^{-1} \cdot \Gamma \left(1 + \frac{1}{p} \right) \end{split}$$

8. Parametric survival models

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

$$\begin{split} E(T|X=x) &= \int_{t=0}^{\infty} S(t|x) dt \\ &= \int_{t=0}^{\infty} S_0(t \cdot \theta(x)) dt \\ &= \int_{u=0}^{\infty} S_0(u) du \cdot \theta(x)^{-1} \\ &= \theta(x)^{-1} \cdot \int_{u=0}^{\infty} S_0(u) du \\ &= \theta(x)^{-1} \cdot \operatorname{E}(T|X=0) \end{split}$$

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:

$$\begin{split} H(t|x) &= H_0(\theta(x) \cdot t) \\ h(t|x) &= \theta(x) \cdot h_0(\theta(x) \cdot t) \end{split}$$

If the base distribution is exponential with parameter λ 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 λ is the intercept and the other coefficients are those of η , 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 η_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 λ is the intercept and the other coefficients are those of η , 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|)
```

8.1.5.2. Weibull parametric model

```
anderson.weib <- survreg(
  formula = surv ~ rx,
  data = anderson,
  dist = "weibull")
summary(anderson.weib)
#>
#> Call:
#> survreg(formula = surv ~ rx, data = anderson, dist = "weibull")
#> Value Std. Error z p
#> (Intercept) 3.516   0.252 13.96 < 2e-16
#> rxstandard -1.267   0.311 -4.08 4.5e-05
#> Log(scale) -0.312   0.147 -2.12   0.034
#>
#> 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 p
#> (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. New York, NY: Springer New York. 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.
- Faraway, Julian J. 2016. Extending the Linear Model with r: Generalized Linear, Mixed Effects and Nonparametric Regression Models. 2nd ed. Chapman; Hall/CRC. https://doi.org/10.1201/9781315382722.
- 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.
- Fox, John. 2015. Applied Regression Analysis and Generalized Linear Models. Sage publications.
- 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.
- Harrell, Frank E. 2015. Regression Modeling Strategies: With Applications to Linear Models, Logistic Regression, and Survival Analysis. 2nd ed. Springer. https://doi.org/10.1007/978-3-319-19425-7.
- James, Gareth, Daniela Witten, Trevor Hastie, Robert Tibshirani, et al. 2013. An Introduction to Statistical Learning. Vol. 112. Springer. https://www.statlearning.com/.
- 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/.
- Kleinman, Ken, and Nicholas J Horton. 2009. SAS and r: Data Management, Statistical Analysis, and Graphics. Chapman; Hall/CRC. https://www.routledge.com/SAS-and-R-Data-Management-Statistical-Analysis-and-Graphics-Second-Edition/Kleinman-Horton/p/book/9781466584495.
- Kuhn, Max, and Julia Silge. 2022. *Tidy Modeling with r.* "O'Reilly Media, Inc.". https://www.tmwr.org/.
- 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.
- McCullagh, Peter, and J. A. Nelder. 1989. Generalized Linear Models. 2nd ed. Routledge. https://www.utstat.toronto.edu/~brunner/oldclass/2201s11/readings/glmbook.pdf.
- 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.
- Nahhas, Ramzi W. n.d. Introduction to Regression Methods for Public Health Using r. CRC Press. https://doi.org/10.1201/9781315382722.
- 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.

- Polin, Richard A, William W Fox, and Steven H Abman. 2011. Fetal and Neonatal Physiology. 4th ed. Elsevier health sciences.
- Rosenman, Ray H, Richard J Brand, C David Jenkins, Meyer Friedman, Reuben Straus, and Moses Wurm. 1975. "Coronary Heart Disease in the Western Collaborative Group Study: Final Follow-up Experience of 8 1/2 Years." *JAMA* 233 (8): 872–77. https://doi.org/10.1001/jama. 1975.03260080034016.
- 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. R for Data Science. "O'Reilly Media, Inc.". https://r4ds.hadley.nz/.

Configuring R

Functions from these packages will be used throughout this document:

```
library(conflicted) # check for conflicting function definitions
# library(printr) # inserts help-file output into markdown output
library(rmarkdown) # Convert R Markdown documents into a variety of formats.
library(pander) # format tables for markdown
library(ggplot2) # graphics
library(ggeasy) # help with graphics
library(ggfortify) # help with graphics
library(dplyr) # manipulate data
library(tibble) # `tibble`s extend `data.frame`s
library(magrittr) # `%>%` and other additional piping tools
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(haven) # import Stata files
```

```
library(latex2exp) # use LaTeX in R code (for figures and tables)
library(fs) # filesystem path manipulations
library(survival) # survival analysis
library(survminer) # survival analysis graphics
library(KMsurv) # datasets from Klein and Moeschberger
library(parameters) # format model output tables for
library(webshot2) # convert interactive content to static for pdf
library(forcats) # functions for categorical variables ("factors")
library(stringr) # functions for dealing with strings
library(lubridate) # functions for dealing with dates and times
```

Here are some R settings I use in this document:

```
rm(list = ls()) # delete any data that's already loaded into R

conflicts_prefer(dplyr::filter)
ggplot2::theme_set(
    ggplot2::theme_bw() +
        # ggplot2::labs(col = "") +
        ggplot2::theme(
        legend.position = "bottom",
        text = ggplot2::element_text(size = 12, family = "serif")))

knitr::opts_chunk$set(message = FALSE)
options('digits' = 4)

panderOptions("big.mark", ",")
pander::panderOptions("table.emphasize.rownames", FALSE)
pander::panderOptions("table.split.table", Inf)
conflicts_prefer(dplyr::filter) # use the `filter()` function from dplyr() by defaul
legend_text_size = 9
```

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.

Exercise A.1 (Examples of binary variables). What are some examples of binary variables 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)

A.2. Key probability distributions

A.2.1. The Bernoulli distribution

Definition A.2 (Bernoulli distribution). The **Bernoulli distribution** family for a random variable X is defined as:

$$\begin{split} \Pr(X = x) &= \mathbb{1}_{x \in \{0,1\}} \pi^x (1 - \pi)^{1 - x} \\ &= \left\{ \begin{matrix} \pi, x = 1 \\ 1 - \pi, x = 0 \end{matrix} \right. \end{split}$$

A.2.2. The Poisson distribution

Definition A.3 (Poisson distribution).

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

A.3. Characteristics of probability distributions

Definition A.4 (Density function). The density function f(t) or p(T = 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:

$$f(t) \stackrel{\mathrm{def}}{=} \frac{\partial}{\partial t} \Pr(T \le t)$$

Definition A.5 (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.6 (Expectation, expected value, population mean). The **expectation**, **expected value**, or **population mean** of a *continuous* random variable X, denoted $\mathbb{E}[X]$, $\mu(X)$, or μ_X , is the weighted mean of X's possible values, weighted by the probability density function of those values:

$$\mathbb{E}[X] = \int_{x \in \mathcal{R}(X)} x \cdot p(X = x) dx$$

The expectation, expected value, or population mean of a discrete random variable X, denoted $\mathbb{E}[X]$, $\mu(X)$, or μ_X , is the mean of X's possible values, weighted by the probability mass function of those values:

$$\mathbb{E}\left[X\right] = \sum_{x \in \mathcal{R}(X)} x \cdot \mathrm{P}(X = x)$$

(c.f. https://en.wikipedia.org/wiki/Expected_value)

Theorem A.1 (Expectation of the Bernoulli distribution). The expectation of a Bernoulli random variable with parameter π is:

 $\mathbb{E}\left[X\right] =\pi$

Proof.

$$\begin{split} \mathbb{E}\left[X\right] &= \sum_{x \in \mathcal{R}(X)} x \cdot \mathrm{P}(X = x) \\ &= \sum_{x \in \{0,1\}} x \cdot \mathrm{P}(X = x) \\ &= (0 \cdot \mathrm{P}(X = 0)) + (1 \cdot \mathrm{P}(X = 1)) \\ &= (0 \cdot (1 - \pi)) + (1 \cdot \pi) \\ &= 0 + \pi \\ &= \pi \end{split}$$

Definition A.7 (Variance). The variance of a random variable X is the expectation of the squared difference between X and $\mathbb{E}[X]$; that is:

$$\operatorname{Var}\left(X\right) \stackrel{\operatorname{def}}{=} \mathbb{E}\left[(X - \mathbb{E}\left[X\right])^2\right]$$

Theorem A.2 (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.8 (Precision). The **precision** of a random variable X, often denoted $\tau(X)$, τ_X , or shorthanded as τ , is the inverse of that random variable's variance; that is:

$$\tau(X) \stackrel{\text{def}}{=} (\operatorname{Var}(X))^{-1}$$

Definition A.9 (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.10 (Covariance). For any two one-dimensional random variables, X, Y:

$$\operatorname{Cov}\left(X,Y\right) \stackrel{\operatorname{def}}{=} \mathbb{E}\left[(X - \mathbb{E}\left[X\right])(Y - \mathbb{E}\left[Y\right])\right]$$

Theorem A.3.

$$Cov((X,Y) = \mathbb{E}[XY] - \mathbb{E}[X]\mathbb{E}[Y]$$

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.11 (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.4 (Alternate expression for variance of a random vector).

$$Var(X) = E[X^{\top}X] - E[X]^{\top}E[X]$$

Proof.

$$\begin{aligned} \operatorname{Var}\left(X\right) &= E[\left(X^{\top} - E[X]^{\top}\right) \left(X - E[X]\right)] \\ &= E[X^{\top}X - E[X]^{\top}X - X^{\top}E[X] + E[X]^{\top}E[X]] \\ &= E[X^{\top}X] - E[X]^{\top}E[X] - E[X]^{\top}E[X] + E[X]^{\top}E[X] \\ &= E[X^{\top}X] - 2E[X]^{\top}E[X] + E[X]^{\top}E[X] \\ &= E[X^{\top}X] - E[X]^{\top}E[X] \end{aligned}$$

Definition A.12 (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.13 (homoskedastic, heteroskedastic). 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.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

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.

¹https://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 μ , 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 μ .

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 θ , often denoted $\epsilon(\hat{\theta})$, or more completely $\epsilon(\hat{\theta}, \theta)$, is the difference between the estimate and its estimand θ ; 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 error²:

$$\mathrm{MSE}\left(\hat{\theta}\right) \stackrel{\mathrm{def}}{=} \mathbb{E}\left[(\epsilon(\hat{\theta}))^2\right]$$

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 θ 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).

$$Bias\left(\widehat{\theta}\right) =\mathbb{E}\left[\widehat{\theta}\right] -\theta$$

 $^{^{2}\}mathrm{I}$ 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:

$$\begin{split} \text{MSE} \left(\hat{\theta} \right) &= \mathbb{E} \left[(\mathbf{e}^{(\hat{\theta})})^2 \right] \\ &= \mathbb{E} \left[(\hat{\theta} - \theta)^2 \right] \\ &= \mathbb{E} \left[\hat{\theta}^2 - 2 \hat{\theta} \theta - \theta^2 \right] \\ &= \mathbb{E} \left[\hat{\theta}^2 \right] - \mathbb{E} \left[2 \hat{\theta} \theta \right] + \mathbb{E} \left[\theta^2 \right] \\ &= \mathbb{E} \left[\hat{\theta}^2 \right] - 2 \mathbb{E} \left[\hat{\theta} \right] \theta + \theta^2 \end{split}$$

$$MSE(\hat{\theta}) = (Bias(\hat{\theta}))^{2} + Var(\hat{\theta})$$

B.3.5.1. Unbiased estimators

Definition B.10 (unbiased estimator). An estimator $\hat{\theta}$ is **unbiased** if Bias $(\hat{\theta}) = 0$.

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:

$$\operatorname{Bias}(\hat{\theta}) = 0$$

$$\mathbb{E}[\hat{\theta}] - \theta = 0$$

$$\mathbb{E}[\hat{\theta}] = \theta$$

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. Estimation

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:

$$\left(SE\left(\hat{\theta}\right)\right)^{2} = MSE\left(\hat{\theta}\right) - \left(Bias\left(\hat{\theta}\right)\right)^{2}$$

B. Estimation

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)

429

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).

Configuring R

Functions from these packages will be used throughout this document:

```
library(conflicted) # check for conflicting function definitions
# library(printr) # inserts help-file output into markdown output
library(rmarkdown) # Convert R Markdown documents into a variety of formats.
library(pander) # format tables for markdown
library(ggplot2) # graphics
library(ggeasy) # help with graphics
library(ggfortify) # help with graphics
```

```
library(dplyr) # manipulate data
library(tibble) # `tibble`s extend `data.frame`s
library(magrittr) # `%>%` and other additional piping tools
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(haven) # import Stata files
library(latex2exp) # use LaTeX in R code (for figures and tables)
library(fs) # filesystem path manipulations
library(survival) # survival analysis
library(survminer) # survival analysis graphics
library(KMsurv) # datasets from Klein and Moeschberger
library(parameters) # format model output tables for
library(webshot2) # convert interactive content to static for pdf
library(forcats) # functions for categorical variables ("factors")
library(stringr) # functions for dealing with strings
library(lubridate) # functions for dealing with dates and times
```

Here are some R settings I use in this document:

```
rm(list = ls()) # delete any data that's already loaded into R

conflicts_prefer(dplyr::filter)
ggplot2::theme_set(
    ggplot2::theme_bw() +
        # ggplot2::labs(col = "") +
    ggplot2::theme(
        legend.position = "bottom",
        text = ggplot2::element_text(size = 12, family = "serif")))
```

```
knitr::opts_chunk$set(message = FALSE)
options('digits' = 4)
panderOptions("big.mark", ",")
pander::panderOptions("table.emphasize.rownames", FALSE)
pander::panderOptions("table.split.table", Inf)
conflicts_prefer(dplyr::filter) # use the `filter()` function from dplyr() by defaul
legend_text_size = 9
```

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 $\mathbf{p}_{\Theta}(\tilde{X})$ be a probability model for the distribution of \tilde{X} with parameter vector Θ .

Then the **likelihood** of parameter value θ , 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:

- $\begin{array}{ll} \bullet & \mathcal{L}(\theta) \\ \bullet & \mathcal{L}(\tilde{x};\theta) \\ \bullet & \mathcal{L}(\theta;\tilde{x}) \\ \bullet & \mathcal{L}_{\tilde{x}}(\theta) \end{array}$

- $\mathcal{L}_{\theta}(\tilde{x})$
- $\mathcal{L}(\tilde{x}|\theta)$

All of these notations mean the same thing.

The likelihood is a function that takes θ (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 $X_1,...,X_n$:

$$\mathcal{L}(\tilde{x}|\theta) = \prod_{i=1}^{n} p(X_i = x_i|\theta) \tag{C.1}$$

Proof.

$$\begin{split} \mathcal{L}(\tilde{x}|\theta) &\stackrel{\text{def}}{=} \mathrm{p}(X_1 = x_1, ..., X_n = x_n|\theta) \\ &= \prod_{i=1}^n \mathrm{p}(X_i = x_i|\theta) \end{split}$$

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 Θ , denoted $\hat{\theta}_{ML}$, is the value of Θ 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 $\mathcal{R}(x)$ 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 θ . However, even for mutually independent data, we quickly run into a problem:

$$\begin{split} \mathcal{L}'(\theta) &= \frac{\partial}{\partial \theta} \mathcal{L}(\theta) \\ &= \frac{\partial}{\partial \theta} \prod_{i=1}^n p(X_i = x_i | \theta) \end{split} \tag{C.3}$$

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 θ , for model $p_{\Theta}(\tilde{X})$ and data $\tilde{X} = \tilde{x}$, is the natural logarithm of the likelihood¹:

¹https://en.wikipedia.org/wiki/Does_exactly_what_it_says_on_the_tin

$$\ell(\theta) \stackrel{\text{def}}{=} \log \left\{ \mathcal{L}(\theta) \right\}$$

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):

$$\ell(x|\theta) = \sum_{i=1}^{n} \log \left\{ p(X = x_i|\theta) \right\} \tag{C.4}$$

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:

$$\ell'(\theta) = \sum_{i=1}^{n} \frac{\partial}{\partial \theta} \log \left\{ p(X = x_i | \theta) \right\}$$
 (C.5)

Proof.

$$\begin{split} \ell'(\theta) &= \frac{\partial}{\partial \theta} \ell(\theta) \\ &= \frac{\partial}{\partial \theta} \sum_{i=1}^n \log \left\{ \mathbf{p}(X = x_i | \theta) \right\} \\ &= \sum_{i=1}^n \frac{\partial}{\partial \theta} \log \left\{ \mathbf{p}(X = x_i | \theta) \right\} \end{split}$$

C.1.6. The score function

The first derivative² 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:

²a.k.a. the gradient³

$$\ell'(\theta) \stackrel{\text{def}}{=} \frac{\partial}{\partial \theta} \ell(\theta)$$

We often skip writing the arguments x and/or θ), so $\ell' \stackrel{\text{def}}{=} \ell'(\tilde{x}; \theta) \stackrel{\text{def}}{=} \ell'(\theta)$. Some statisticians use U or S instead of ℓ' . I prefer ℓ' . 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:

- $\mathcal{I}(\theta) \stackrel{\text{def}}{=} \mathbb{E}\left[I(\tilde{X}; \theta)\right]$
- $I(\tilde{X}, \theta) \stackrel{\text{def}}{=} -\ell''(\tilde{X}; \theta)$

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:

$$\widehat{\mathrm{SE}}\left(\widehat{\boldsymbol{\theta}}_{k}\right) = \sqrt{\left[\left(\widehat{\boldsymbol{\mathcal{I}}}\left(\widehat{\boldsymbol{\theta}}_{\mathrm{ML}}\right)\right)^{-1}\right]_{kk}}$$

⁴I might sometimes switch the order of x, θ ; this is unintentional and not meaningful.

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).

$$\mathfrak{I} \stackrel{\text{def}}{=} \mathfrak{I}(\theta) \stackrel{\text{def}}{=} Cov\left(\ell'|\theta\right) = E[\ell'{\ell'}^{\intercal}] - E[\ell'] \; E[\ell']^{\intercal}$$

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,

$$\begin{split} \mathbb{E}\left[\ell'\right] &\stackrel{\text{def}}{=} \int_{x \in \mathcal{R}(x)} \ell'(x,\theta) \mathbf{p}(X=x|\theta) dx \\ &= \int_{x \in \mathcal{R}(X)} \left(\frac{\partial}{\partial \theta} \log \left\{\mathbf{p}(X=x|\theta)\right\}\right) \mathbf{p}(X=x|\theta) dx \\ &= \int_{x \in \mathcal{R}(X)} \frac{\frac{\partial}{\partial \theta} \mathbf{p}(X=x|\theta)}{\mathbf{p}(X=x|\theta)} \mathbf{p}(X=x|\theta) dx \\ &= \int_{x \in \mathcal{R}(X)} \frac{\partial}{\partial \theta} \mathbf{p}(X=x|\theta) dx \end{split}$$

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 $\mathbb{E}[\ell']$ and $\mathbb{E}[\ell'\ell']$ are functions of θ 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

$$\mathcal{I}\left(\theta\right) = \mathbb{E}\left[\ell'{\ell'}^{\top}\right]$$

Moreover, for those distributions (called the "exponential family"), we have:

$$\mathfrak{I} = -\mathbb{E}\left[\ell''\right] = \mathbb{E}\left[-\ell''\right]$$

(see Dobson and Barnett (2018), §3.17), where

$$\ell'' \stackrel{\mathrm{def}}{=} \frac{\partial}{\partial \theta} \ell'^{(x,\theta)^{\top}} = \frac{\partial}{\partial \theta} \frac{\partial}{\partial \theta^{\top}} \ell(x,\theta)$$

is the $p \times p$ matrix whose elements are:

$$\ell_{ij}'' \stackrel{\text{def}}{=} \frac{\partial}{\partial \theta_{i}} \frac{\partial}{\partial \theta_{j}} \log \left\{ p \left(X = x \mid \theta \right) \right\}$$

 ℓ'' is 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).

⁵named after mathematician Otto Hesse⁶

Key point

The asymptotics of MLEs gives us $\hat{\theta}_{ML} \sim N(\theta, \Im^{-1}(\theta))$, 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. Iterative maximization

Note that later, when we are trying to find MLEs for likelihoods which we can't easily differentiate, we will "hill-climb" using the Newton-Raphson algorithm:

$$\begin{split} \hat{\theta}^* &\leftarrow \hat{\theta}^* + \left(I\left(\tilde{y}; \hat{\theta}^* \right) \right)^{-1} \ell'\left(\tilde{y}; \hat{\theta}^* \right) \\ &= \hat{\theta}^* - \left(\ell''\left(\tilde{y}; \hat{\theta}^* \right) \right)^{-1} \ell'\left(\tilde{y}; \hat{\theta}^* \right) \end{split}$$

The reasoning for this algorithm is that we can approximate the the score function using the first-order Taylor polynomial⁷:

$$\begin{split} \ell'(\theta) &\approx \ell'^*(\theta) \\ &\stackrel{\text{def}}{=} \ell'(\hat{\theta}^*) + \ell''(\hat{\theta}^*)(\theta - \hat{\theta}^*) \end{split}$$

 $^{^{7} \}rm https://en.wikipedia.org/wiki/Taylor\%27s_theorem$

The approximate score function, $\ell'^*(\theta)$, is a linear function of θ , so it is easy to solve the corresponding approximate score equation, $\ell'^*(\theta) = 0$, for θ :

$$\theta = \hat{\theta}^* - \ell'(\hat{\theta}^*) \cdot \left(\ell''(\hat{\theta}^*)\right)^{-1}$$

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)):

$$I_e(\theta, y) \stackrel{\mathrm{def}}{=} \sum_{i=1}^n \ell_i' \; {\ell_i'}^\top - \frac{1}{n} {\ell'} {\ell'}^\top$$

where ℓ_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.f. https://en.wikipedia.org/wiki/Newton%27s method in optimization

C.1.10. Quantifying (un)certainty of MLEs

C.1.10.1. Confidence intervals for MLEs

An asymptotic approximation of a 95% confidence interval for θ_k is

$$\hat{\theta}_{\mathrm{ML}} \pm z_{0.975} \times \widehat{\mathrm{SE}} \left(\hat{\theta}_k \right)$$

where z_{β} the β quantile of the standard Gaussian distribution.

C.1.10.2. p-values and hypothesis tests for MLEs

(to add)

C.1.10.3. 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.1.10.4. 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") +
expand_limits(y = 0) +
theme(axis.text.x = element_text(vjust = .5, angle = 45))
```

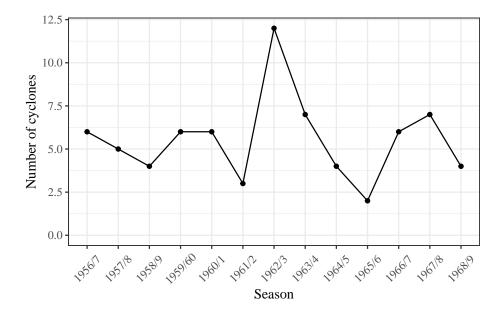


Figure C.1.: Number of tropical cyclones per season in northeastern Australia, 1956-1969

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) +
  xlab("Number of cyclones") +
  ylab("Count (number of seasons)")
```

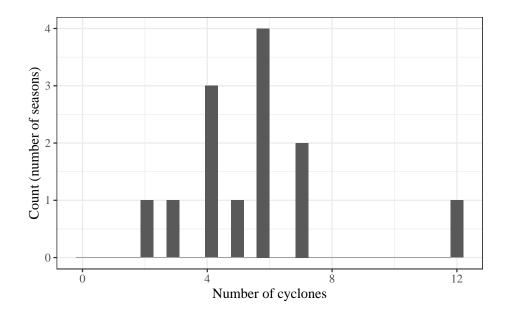


Figure C.2.: Bar plot of cyclones per season

```
n = nrow(cyclones)
sumx = cyclones |> pull(number) |> sum()
```

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]	

```
xbar = cyclones |> pull(number) |> mean()
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.

$$P(Y=y) = \frac{\lambda^y e^{-\lambda}}{y!} \tag{C.6}$$

C.2.4. Estimating the model parameters using maximum likelihood

Now, we can estimate the parameter λ 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, λ :

$$\theta = (\lambda)$$

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] = λ
Population variance: Var(X) = λ

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 λ .

Solution.

```
lik = function(lambda, y = cyclones$number, n = length(y))
{
lambda^sum(y) * exp(-n*lambda) / prod(factorial(y))
}

library(ggplot2)
lik_plot =
ggplot() +
geom_function(fun = lik, n = 1001) +
xlim(min(cyclones$number), max(cyclones$number)) +
ylab("likelihood") +
xlab('lambda')

print(lik_plot)
```

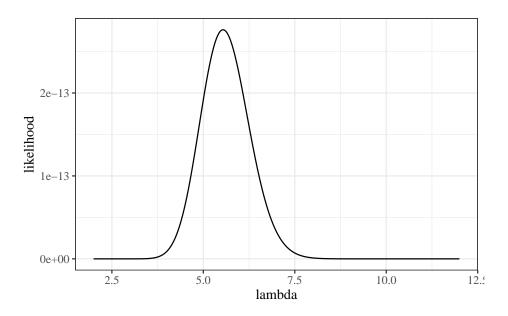


Figure C.3.: Likelihood of Dobson cyclone data

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 λ .

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)) +
ylab("log-likelihood") +
xlab('lambda')
ll_plot
```



Figure C.4.: log-likelihood of Dobson cyclone data

C.2.4.1. The score function

Exercise C.10. Derive the score function for the dataset.

Solution. The score function is the first derivative of the log-likelihood:

$$\begin{split} \ell'(\lambda;\tilde{x}) &= \frac{\partial}{\partial \lambda} \sum_{i=1}^n x_i \log \left\{ \lambda \right\} - n\lambda - \sum_{i=1}^n \log \left\{ x_i ! \right\} \\ &= \frac{\partial}{\partial \lambda} \sum_{i=1}^n x_i \log \left\{ \lambda \right\} - \frac{\partial}{\partial \lambda} n\lambda - \frac{\partial}{\partial \lambda} \sum_{i=1}^n \log \left\{ x_i ! \right\} \\ &= \sum_{i=1}^n x_i \frac{\partial}{\partial \lambda} \log \left\{ \lambda \right\} - n \frac{\partial}{\partial \lambda} \lambda - \sum_{i=1}^n \frac{\partial}{\partial \lambda} \log \left\{ x_i ! \right\} \\ &= \sum_{i=1}^n x_i \frac{1}{\lambda} - n - 0 \\ &= \frac{1}{\lambda} \sum_{i=1}^n x_i - n \\ &= \left(\frac{1}{\lambda} n \bar{x} \right) - n \\ &= \left(\frac{1}{\lambda} 72 \right) - 13 \end{split}$$

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)) +
ylab("l'(lambda)") +
```

```
xlab('lambda') +
geom_hline(yintercept = 0, col = 'red')
```



Figure C.5.: score function of Dobson cyclone data

C.2.4.2. The Hessian matrix

Exercise C.12. Derive the Hessian matrix.

Solution. The Hessian function for an iid sample is the 2nd derivative(s) of the log-likelihood:

$$\begin{split} \ell''(\lambda;\tilde{x}) &= \frac{\partial}{\partial \lambda} \left(\frac{1}{\lambda} \sum_{i=1}^{n} x_i - n \right) \\ &= \frac{\partial}{\partial \lambda} \frac{1}{\lambda} \sum_{i=1}^{n} x_i - \frac{\partial}{\partial \lambda} n \\ &= -\frac{1}{\lambda^2} \sum_{i=1}^{n} x_i \\ &= -\frac{1}{\lambda^2} n \bar{x} \\ &= -\frac{1}{\lambda^2} \cdot 72 \end{split}$$

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)) +

ylab("l''(lambda)") +
xlab('lambda') +
geom_hline(yintercept = 0, col = 'red')
```

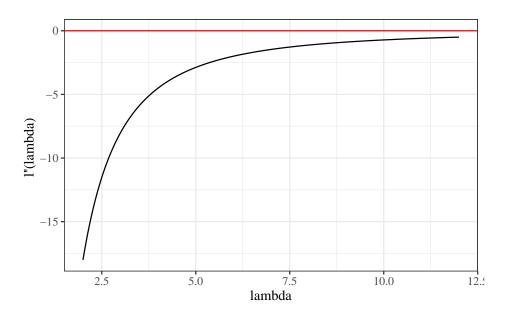


Figure C.6.: Hessian function of Dobson cyclone data

Exercise C.14. Write the score equation (estimating equation).

Solution.

$$\ell'(\lambda;\tilde{x})=0$$

Exercise C.15. Solve the estimating equation for λ :

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.

$$\begin{split} \ell''(\tilde{\lambda};\tilde{x}) &= -\frac{1}{\tilde{\lambda}^2} n \bar{x} \\ &= -\frac{1}{\bar{x}^2} n \bar{x} \\ &= -\frac{n}{\bar{x}} \\ &< 0 \end{split}$$

Exercise C.17. Find the MLE of λ .

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 $\mathcal{L}(\lambda; \tilde{x})$:

$$\hat{\lambda}_{\mathrm{ML}} = \bar{x} = 5.5385$$

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')
```

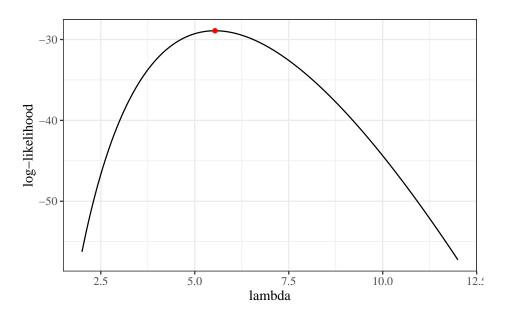


Figure C.7.: log-likelihood of Dobson cyclone data with MLE

C.2.4.3. Information matrices

```
obs_inf = function(...) -hessian(...)
ggplot() +
geom_function(fun = obs_inf, n = 1001) +
xlim(min(cyclones$number), max(cyclones$number)) +
ylab("I(lambda)") +
xlab('lambda') +
geom_hline(yintercept = 0, col = 'red')
```

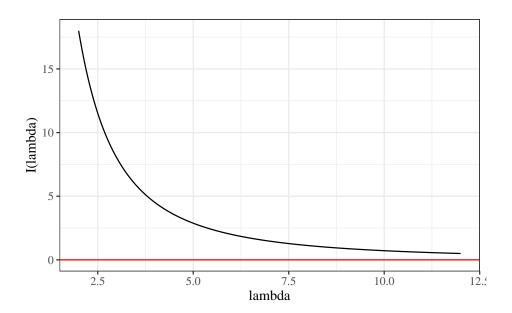


Figure C.8.: Observed information function of Dobson cyclone data

Example C.1 (Finding the MLE using the Newton-Raphson algorithm).

We found that the MLE was $\hat{\lambda} = \bar{x}$, by solving the score equation $\ell'(\lambda) = 0$ for λ .

What if we hadn't been able to solve the score equation?

Then we could start with some initial guess $\hat{\lambda}^*$, such as $\hat{\lambda}^* = 3$, and use the Newton-Raphson algorithm.

```
# specify initial guess:
cur_lambda_est = 3
```

In Exercise C.10, we found that the score function was:

$$\ell'(\lambda;\tilde{x}) = \left(\frac{72}{\lambda}\right) - n$$

In Exercise C.12, we found that the Hessian was:

$$\ell''(\lambda;\tilde{x}) = -\frac{72}{\lambda^2}$$

So we can approximate the the score function using the first-order Taylor polynomial 8 :

$$\begin{split} \ell'(\lambda) &\approx \ell'^*(\lambda) \\ &\stackrel{\text{def}}{=} \ell'(\hat{\lambda}^*) + \ell''(\hat{\lambda}^*)(\lambda - \hat{\lambda}^*) \\ &= \left(\frac{72}{\hat{\lambda}^*} - n\right) + \left(-\frac{72}{\left(\hat{\lambda}^*\right)^2}\right)(\lambda - \hat{\lambda}^*) \end{split}$$

Figure C.9 compares the true score function and the approximate score function at $\hat{\lambda}^* = 3$.

⁸https://en.wikipedia.org/wiki/Taylor%27s_theorem

```
approx_score = function(lambda, lhat, ...)
  score(lambda = lhat, ...) +
  hessian(lambda = lhat, ...) * (lambda - lhat)
}
point_size = 5
plot1 = ggplot() +
geom_function(
 fun = score,
  aes(col = "true score function"),
  n = 1001) +
geom_function(
  fun = approx_score,
  aes(col = "approximate score function"),
  n = 1001,
  args = list(lhat = cur_lambda_est)) +
geom_point(
 size = point_size,
  aes(x = cur_lambda_est, y = score(lambda = cur_lambda_est),
      col = "current estimate")
) +
geom_point(
size = point_size,
aes(
x = xbar,
y = 0,
col = "true MLE"
) +
xlim(min(cyclones$number), max(cyclones$number)) +
ylab("1'(lambda)") +
```



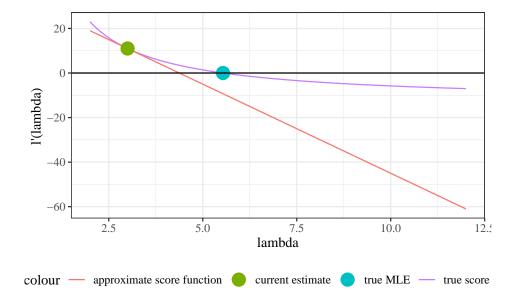


Figure C.9.: score function of Dobson cyclone data and approximate score function

This is equivalent to estimating the log-likelihood with a second-order Taylor polynomial:

$$\ell^*(\lambda) = \ell(\hat{\lambda}^*) + (\lambda - \hat{\lambda}^*)\ell'(\hat{\lambda}^*) + \frac{1}{2}\ell''(\hat{\lambda}^*)(\lambda - \hat{\lambda}^*)^2$$

```
approx_loglik = function(lambda, lhat, ...)
loglik(lambda = lhat, ...) +
score(lambda = lhat, ...) * (lambda - lhat) +
1/2 * hessian(lambda = lhat, ...) * (lambda - lhat)^2
}
plot_loglik = ggplot() +
geom_function(
 fun = loglik,
  aes(col = "true log-likelihood"),
 n = 1001) +
geom_function(
 fun = approx_loglik,
  aes(col = "approximate log-likelihood"),
  n = 1001,
  args = list(lhat = cur_lambda_est)) +
geom_point(
  size = point_size,
  aes(x = cur_lambda_est, y = loglik(lambda = cur_lambda_est),
      col = "current estimate")
) +
geom_point(
size = point_size,
aes(
x = xbar,
y = loglik(xbar),
col = "true MLE"
)
) +
xlim(min(cyclones$number) - 1, max(cyclones$number)) +
ylab("1'(lambda)") +
xlab('lambda')
```

print(plot_loglik)

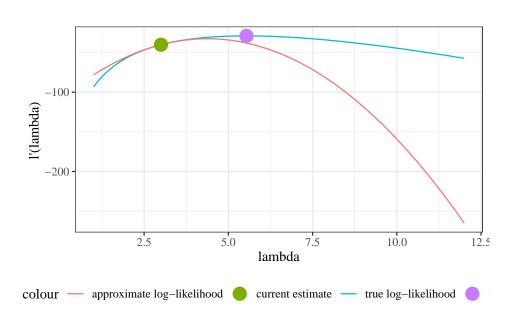


Figure C.10.: log-likelihood of Dobson cyclone data and approximate log-likelihood function

The approximate score function, $\ell'^*(\lambda)$, is a linear function of λ , so it is easy to solve the corresponding approximate score equation, $\ell'^*(\lambda) = 0$, for λ :

$$\begin{split} \lambda &= \hat{\lambda}^* - \ell'(\hat{\lambda}^*) \cdot \left(\ell''(\hat{\lambda}^*)\right)^{-1} \\ &= 4.375 \end{split}$$

```
new_lambda_est <-
   cur_lambda_est -
   score(cur_lambda_est) * hessian(cur_lambda_est)^-1</pre>
```

```
plot2 = plot1 +
geom_point(
size = point_size,
aes(
x = new_lambda_est,
y = 0,
col = "new estimate"
)) +
geom_segment(
arrow = grid::arrow(),
linewidth = 2,
alpha = .7,
aes(
x = cur_lambda_est,
y = approx_score(
lhat = cur_lambda_est,
lambda = cur_lambda_est),
xend = new_lambda_est,
yend = 0,
col = "update"
)
print(plot2)
```



Figure C.11.: score function of Dobson cyclone data and approximate score function

So we update $\hat{\lambda}^* \leftarrow 4.375$ and repeat our estimation process:

```
plot2 +
geom_function(
  fun = approx_score,
  aes(col = "new approximate score function"),
  n = 1001,
  args = list(lhat = new_lambda_est)) +
geom_point(
  size = point_size,
  aes(x = new_lambda_est, y = score(lambda = new_lambda_est),
```

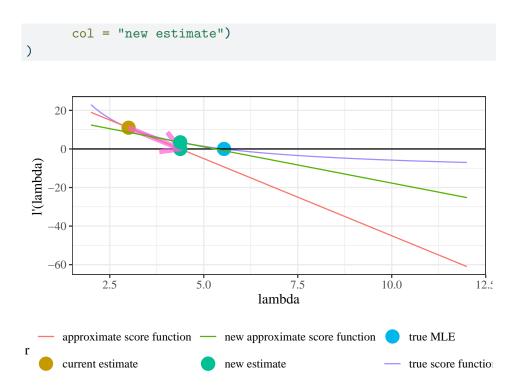


Figure C.12.: score function of Dobson cyclone data and approximate score function

We repeat this process until the likelihood converges:

Compare with Exercise C.17

Table C.3.: Convergence of Newton-Raphson Algorithm for finding MLE of cyclone data

```
library(tibble)
cur_lambda_est = 3 # restarting
diff_loglik = Inf
tolerance = 10^-4
max_iter = 100
NR_info = tibble(
 iteration = 0,
 lambda = cur_lambda_est |> num(digits = 4),
 likelihood = lik(cur_lambda_est),
  `log(likelihood)` = loglik(cur_lambda_est) |> num(digits = 4),
 score = score(cur_lambda_est),
 hessian = hessian(cur_lambda_est)
for (cur_iter in 1:max_iter)
new_lambda_est <-
   cur_lambda_est - score(cur_lambda_est) * hessian(cur_lambda_est)^-1
diff_loglik = loglik(new_lambda_est) - loglik(cur_lambda_est)
new_NR_info = tibble(
 iteration = cur_iter,
 lambda = new_lambda_est,
 likelihood = lik(new_lambda_est),
  `log(likelihood)` = loglik(new_lambda_est),
 score = score(new_lambda_est),
 hessian = hessian(new_lambda_est),
  `diff(loglik)` = diff_loglik
NR_info = NR_info |> bind_rows(new_NR_info)
                            469
cur_lambda_est = new_lambda_est
if(abs(diff_loglik) < tolerance) break</pre>
}
NR_info
#> # A tibble: 6 x 7
#> iteration lambda likelihood `log(likelihood)` score hessian `diff(loglik)`
#> <dbl> <num:.> <dbl> <num:.4!> <dbl> <dbl>
                                                                          <dbl>
        0 3.0000 4.00e-18
                                                                      NA
#> 1
                                       -40.0610 1.1 e+ 1 -8
#> 2
          1 4.3750 4.33e-14
                                       -30.7708 3.46e+ 0 -3.76
                                                                      9.29e+ 0
```

```
ll_plot +
geom_segment(
data = NR_info,
arrow = grid::arrow(),
# linewidth = 2,
alpha = .7,
aes(
x = lambda,
xend = lead(lambda),
y = `log(likelihood)`,
yend = lead(`log(likelihood)`),
col = factor(iteration)
),
)
```

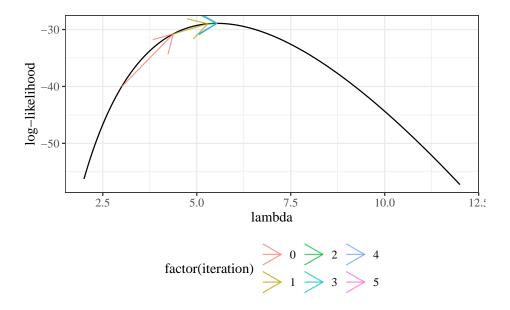


Figure C.13.: Newton-Raphson algorithm for finding MLE of model C.6 for cyclone data

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:

$$\begin{split} \ell & \propto -\frac{n}{2} \log \left\{ \sigma^2 \right\} - \frac{1}{2} \sum_{i=1}^n \frac{(x_i - \mu)^2}{\sigma^2} \\ & = -\frac{n}{2} \log \left\{ \sigma^2 \right\} - \frac{1}{2\sigma^2} \sum_{i=1}^n x_i^2 - 2x_i \mu + \mu^2 \end{split}$$

C.3.1. The score function

$$\ell'(x,\theta) \stackrel{\mathrm{def}}{=} \frac{\partial}{\partial \theta} \ell(x,\theta) = \left(\begin{array}{c} \frac{\partial}{\partial \mu} \ell(\theta;x) \\ \frac{\partial}{\partial \sigma^2} \ell(\theta;x) \end{array} \right) = \left(\begin{array}{c} \ell'_{\mu}(\theta;x) \\ \ell'_{\sigma^2}(\theta;x) \end{array} \right)$$

 $\ell'(x,\theta)$ 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 μ

$$\begin{split} \frac{d\ell}{d\mu} &= -\frac{1}{2} \sum_{i=1}^{n} \frac{-2(x_i - \mu)}{\sigma^2} \\ &= \frac{1}{\sigma^2} \left[\left(\sum_{i=1}^{n} x_i \right) - n\mu \right] \end{split}$$

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 σ^2

• Reparametrizing the Gaussian distribution

When solving for $\hat{\sigma}_{ML}$, you can treat σ^2 as an atomic variable (don't differentiate with respect to σ or things get messy). In fact, you can replace σ^2 with $1/\tau$ and differentiate with respect to τ instead, and the process might be even easier.

$$\begin{split} \frac{d\ell}{d\sigma^2} &= \frac{\partial}{\partial \sigma^2} \left(-\frac{n}{2} \log \left\{ \sigma^2 \right\} - \frac{1}{2} \sum_{i=1}^n \frac{\left(x_i - \mu \right)^2}{\sigma^2} \right) \\ &= -\frac{n}{2} \left(\sigma^2 \right)^{-1} + \frac{1}{2} \left(\sigma^2 \right)^{-2} \sum_{i=1}^n \left(x_i - \mu \right)^2 \end{split}$$

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:

$$\begin{split} \frac{d^2\ell}{\left(d\sigma^2\right)^2} &= \frac{\partial}{\partial\sigma^2} \left\{ -\frac{n}{2} \left(\sigma^2\right)^{-1} + \frac{1}{2} \left(\sigma^2\right)^{-2} \sum_{i=1}^n \left(x_i - \mu\right)^2 \right\} \\ &= \left\{ -\frac{n}{2} \frac{\partial}{\partial\sigma^2} \left(\sigma^2\right)^{-1} + \frac{1}{2} \frac{\partial}{\partial\sigma^2} \left(\sigma^2\right)^{-2} \sum_{i=1}^n \left(x_i - \mu\right)^2 \right\} \\ &= \left\{ \frac{n}{2} \left(\sigma^2\right)^{-2} - \left(\sigma^2\right)^{-3} \sum_{i=1}^n \left(x_i - \mu\right)^2 \right\} \\ &= \left(\sigma^2\right)^{-2} \left\{ \frac{n}{2} - \left(\sigma^2\right)^{-1} \sum_{i=1}^n \left(x_i - \mu\right)^2 \right\} \end{split}$$

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:

$$\begin{split} \frac{d^2\ell}{d\mu\;d\sigma^2} &= \frac{\partial}{\partial\mu} \left\{ -\frac{n}{2} \left(\sigma^2\right)^{-1} + \frac{1}{2} \left(\sigma^2\right)^{-2} \sum_{i=1}^n \left(x_i - \mu\right)^2 \right\} \\ &= \frac{1}{2} \left(\sigma^2\right)^{-2} \frac{\partial}{\partial\mu} \sum_{i=1}^n \left(x_i - \mu\right)^2 \\ &= \frac{1}{2} \left(\sigma^2\right)^{-2} \sum_{i=1}^n -2(x_i - \mu) \\ &= -\left(\sigma^2\right)^{-2} \sum_{i=1}^n \left(x_i - \mu\right) \end{split}$$

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:

$$I^{-1} = \frac{1}{ad} \begin{bmatrix} d & 0 \\ 0 & a \end{bmatrix} = \begin{bmatrix} \frac{1}{a} & 0 \\ 0 & \frac{1}{d} \end{bmatrix}$$

$$I^{-1} = \begin{bmatrix} \frac{\hat{\sigma}^2}{n} & 0 \\ 0 & \frac{2(\hat{\sigma}^2)^2}{n} \end{bmatrix}$$

See Casella and Berger (2002) p322, example 7.2.12.

To prove it's a maximum, we need:

- $\ell' = 0$
- At least one diagonal element of ℓ'' is negative.
- Determinant of ℓ'' is positive.

C.4. Example: hormone therapy study

Now, we're going to analyze some real-world data using a Gaussian model, and then we're going to do a simulation to examine the properties of maximum likelihood estimation for that Gaussian model.

Here we look at the "heart and estrogen/progestin study" (HERS), a clinical trial of hormone therapy for prevention of recurrent heart attacks and death among 2,763 post-menopausal women with existing coronary heart disease (CHD) (Hulley et al. 1998).

We are going to model the distribution of fasting glucose among nondiabetics who don't exercise.

```
# load the data directly from a UCSF website
hers = haven::read_dta(
  paste0( # I'm breaking up the url into two chunks for readability
    "https://regression.ucsf.edu/sites/g/files",
    "/tkssra6706/f/wysiwyg/home/data/hersdata.dta"
  )
)
```

Table C.4.: HERS dataset

```
hers |> head()
#> # A tibble: 6 x 37
#>
     ΗТ
                     age raceth nonwhite smoking drinkany exercise physact globrat
     <dbl+lbl>
                   <dbl> <dbl+1> <dbl+1> <dbl+1> <dbl+1> <dbl+1> <dbl+1> <dbl+1>
#> 1 0 [placebo]
                      70 2 [Afr~ 1 [yes]
                                           0 [no] 0 [no]
                                                            0 [no]
                                                                     5 [muc~ 3 [goo~
#> 2 0 [placebo]
                      62 2 [Afr~ 1 [yes]
                                                            0 [no]
                                                                     1 [muc~ 3 [goo~
                                           0 [no]
                                                   0 [no]
#> 3 1 [hormone t~
                      69 1 [Whi~ 0 [no]
                                           0 [no]
                                                   0 [no]
                                                            0 [no]
                                                                     3 [abo~ 3 [goo~
                                                                     1 [muc~ 3 [goo~
#> 4 0 [placebo]
                      64 1 [Whi~ 0 [no]
                                           1 [yes] 1 [yes]
                                                            0 [no]
#> 5 0 [placebo]
                      65 1 [Whi~ 0 [no]
                                           0 [no]
                                                   0 [no]
                                                            0 [no]
                                                                     2 [som~ 3 [goo~
#> 6 1 [hormone t~
                      68 2 [Afr~ 1 [yes] 0 [no] 1 [yes] 0 [no]
                                                                     3 [abo~ 3 [goo~
#> # i 28 more variables: poorfair <dbl+lbl>, medcond <dbl>, htnmeds <dbl+lbl>,
#> #
       statins <dbl+lbl>, diabetes <dbl+lbl>, dmpills <dbl+lbl>,
#> #
       insulin <dbl+lbl>, weight <dbl>, BMI <dbl>, waist <dbl>, WHR <dbl>,
       glucose <dbl>, weight1 <dbl>, BMI1 <dbl>, waist1 <dbl>, WHR1 <dbl>,
#> #
       glucose1 <dbl>, tchol <dbl>, LDL <dbl>, HDL <dbl>, TG <dbl>, tchol1 <dbl>,
#> #
      LDL1 <dbl>, HDL1 <dbl>, TG1 <dbl>, SBP <dbl>, DBP <dbl>, age10 <dbl>
#> #
```

```
n.obs = 100 \text{ # we're going to take a small subset of the data to look at;}
# if we took the whole data set, the likelihood function would be hard to
# graph nicely
library(dplyr)
data1 =
  hers |>
  filter(
    diabetes == 0,
    exercise == 0) >
  head(n.obs)
glucose_data =
  data1 |>
  pull(glucose)
library(ggplot2)
library(ggeasy)
plot1 =
  data1 |>
  ggplot(aes(x = glucose)) +
  geom_histogram(aes(x = glucose, after_stat(density))) +
  theme_classic() +
  easy_labs()
print(plot1)
```



Looks somewhat plausibly Gaussian. Good enough for this example!

C.4.1. Find the MLEs

```
mu_hat = mean(glucose_data)
sigma_sq_hat = mean((glucose_data - mean(glucose_data))^2)
```

Our MLEs are:

- $\hat{\mu} = 98.66$
- $\hat{\sigma}^2 = 104.7444$

Here's the estimated distribution, superimposed on our histogram:

```
plot1 +
  geom_function(
   fun = function(x) dnorm(x, mean = mu_hat, sd = sqrt(sigma_sq_hat)),
   col = "red"
)
```



Looks like a somewhat decent fit? We could probably do better, but that's for another time.

C.4.2. Construct the likelihood and log-likelihood functions

it's often computationally more effective to construct the log-likelihood first and then exponentiate it to get the likelihood

```
loglik = function(
   mu, # I'm assigning default values, which the function will use
    # unless we tell it otherwise
    sigma = sd(x), # note that you can define some defaults based on other arguments
   x = glucose_data,
   n = length(x)
)
{
 normalizing_constants = -n/2 * \log((sigma^2) * 2 * pi)
  likelihood_kernel = - 1/(2 * sigma^2) *
      # I have to do this part in a somewhat complicated way
      # so that we can pass in vectors of possible values of mu
      # and get the likelihood for each value;
      # for the binomial case it's easier
      sum(x^2) - 2 * sum(x) * mu + n * mu^2
 answer = normalizing_constants + likelihood_kernel
 return(answer)
}
# `...` means pass any inputs to lik() along to loglik()
lik = function(...) exp(loglik(...))
```

C.4.3. Graph the Likelihood as a function of μ

```
(fixing \sigma^2 at \hat{\sigma}^2 = 104.7444)
```

```
ggplot() +
  geom_function(fun = function(x) lik(mu = x, sigma = sigma_sq_hat)) +
  xlim(mean(glucose_data) + c(-1,1) * sd(glucose_data)) +
  xlab("possible values of mu") +
  ylab("likelihood") +
  geom_vline(xintercept = mean(glucose_data), col = "red")
```



C.4.4. Graph the Log-likelihood as a function of μ

```
(fixing \sigma^2 at \hat{\sigma}^2 = 104.7444)
```

```
ggplot() +
  geom_function(fun = function(x) loglik(mu = x, sigma = sigma_sq_hat)) +
  xlim(mean(glucose_data) + c(-1,1) * sd(glucose_data)) +
```

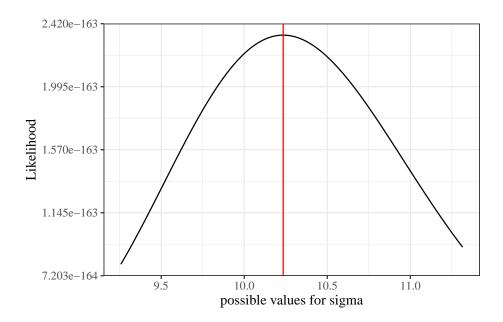
```
xlab("possible values of mu") +
ylab('log(likelihood)') +
geom_vline(xintercept = mean(glucose_data), col = "red")
```



C.4.5. Likelihood and log-likelihood for σ , conditional on $\mu = \hat{\mu}$:

```
ggplot() +
  geom_function(fun = function(x) lik(sigma = x, mu = mean(glucose_data))) +
  xlim(sd(glucose_data) * c(.9,1.1)) +
  geom_vline(
     xintercept = sd(glucose_data) * sqrt(n.obs - 1)/sqrt(n.obs),
     col = "red") +
```

```
xlab("possible values for sigma") +
ylab('Likelihood')
```



```
ggplot() +
  geom_function(
    fun = function(x) loglik(sigma = x, mu = mean(glucose_data))
) +
  xlim(sd(glucose_data) * c(0.9, 1.1)) +
  geom_vline(
    xintercept =
      sd(glucose_data) * sqrt(n.obs - 1) / sqrt(n.obs),
    col = "red") +
  xlab("possible values for sigma") +
  ylab("log(likelihood)")
```



C.4.6. Standard errors by sample size:

```
se.mu.hat = function(n, sigma = sd(glucose_data)) sigma/sqrt(n)
ggplot() +
  geom_function(fun = se.mu.hat) +
  scale_x_continuous(trans = "log10", limits = c(10, 10^5), name = "Sample size") +
  ylab("Standard error of mu (mg/dl)") +
  theme_classic()
```



C.4.7. Simulations

C.4.7.1. Create simulation framework

Here's a function that performs a single simulation of a Gaussian modeling analysis:

```
do_one_sim = function(
    n = 100,
    mu = mean(glucose_data),
    mu0 = mean(glucose_data) * 0.9,
    sigma2 = var(glucose_data),
    return_data = FALSE # if this is set to true, we will create a list() containing
    # the analytic results and the vector of simulated data
)
```

```
{
  # generate data
 x = rnorm(n = 100, mean = mu, sd = sqrt(sigma2))
  # analyze data
 mu_hat = mean(x)
  sigmahat = sd(x)
  se_hat = sigmahat/sqrt(n)
  confint = mu_hat + c(-1, 1) * se_hat * qt(.975, df = n - 1)
  tstat = abs(mu_hat - mu0) / se_hat
  pval = pt(df = n - 1, q = tstat, lower = FALSE) * 2
  confint_covers = between(mu, confint[1], confint[2])
  test_rejects = pval < 0.05</pre>
  # if you want spaces, hyphens, or characters in your column names, use "", '', or
  to_return = tibble(
    "mu-hat" = mu_hat,
    "sigma-hat" = sigmahat,
    "se_hat" = se_hat,
    "confint_left" = confint[1],
    "confint_right" = confint[2],
    "tstat" = tstat,
    "pval" = pval,
    "confint covers true mu" = confint_covers,
    "test rejects null hypothesis" = test_rejects
  if(return_data)
   return(
      list(
        data = x,
```

```
results = to_return))
} else
{
   return(to_return)
}
```

Let's see what this function outputs for us:

```
do_one_sim()
#> # A tibble: 1 x 9
    `mu-hat` `sigma-hat` se_hat confint_left confint_right tstat
                                                                    pval
#>
       <dbl>
                <dbl> <dbl>
                                      <dbl>
                                                   <dbl> <dbl>
                                                                   <dbl>
#> 1
        97.2
                    9.67 0.967
                                       95.3
                                                    99.1 8.70 7.61e-14
#> # i 2 more variables: `confint covers true mu` <lgl>,
    `test rejects null hypothesis` <lgl>
```

Looks good!

Now let's check it against the t.test() function from the stats package:

```
set.seed(1)
mu = mean(glucose_data)
mu0 = 80
sim.output = do_one_sim(mu0 = mu0, return_data = TRUE)
our_results =
   sim.output$results |>
   mutate(source = "`do_one_sim()`")

results_t.test = t.test(sim.output$data, mu = mu0)
```

```
results2 =
 tibble(
   source = "`stats::t.test()`",
    "mu-hat" = results_t.test$estimate,
    "sigma-hat" = results_t.test$stderr*sqrt(length(sim.output$data)),
   "se_hat" = results_t.test$stderr,
   confint_left = results_t.test$conf.int[1],
   confint_right = results_t.test$conf.int[2],
   tstat = results_t.test$statistic,
   pval = results_t.test$p.value,
   "confint covers true mu" = between(mu, confint_left, confint_right),
     `test rejects null hypothesis` = pval < 0.05
  )
comparison =
 bind_rows(
   our_results,
   results2
 ) |>
 relocate(
   "source",
    .before = everything()
  )
comparison
#> # A tibble: 2 x 10
    source
            `mu-hat` `sigma-hat` se_hat confint_left confint_right tstat
                                                                               pval
    <chr>
                 <dbl>
                            <dbl> <dbl>
                                                 <dbl>
                                                               <dbl> <dbl>
                                                                               <dbl>
#> 1 `do_one~
                             9.24 0.924
                                                  97.9
                                                                102. 21.4 6.23e-39
                  99.8
                              9.24 0.924
#> 2 `stats:~
                 99.8
                                                  97.9
                                                                102. 21.4 6.23e-39
#> # i 2 more variables: `confint covers true mu` <lgl>,
#> # `test rejects null hypothesis` <lgl>
```

Looks like we got it right!

C.4.7.2. Run 1000 simulations

Here's a function that calls the previous function n_sims times and summarizes the results:

```
do_n_sims = function(
   n_sims = 1000,
    ... # this symbol means "allow additional arguments to be passed on to the `do_s
)
{
  sim_results = NULL # we're going to create a "tibble" of results,
  # row by row (slightly different from the hint on the homework)
  for (i in 1:n_sims)
  {
    set.seed(i)
    current_results =
      do_one_sim(...) |> # here's where the simulation actually gets run
      mutate(
        sim_number = i
      ) |>
      relocate(sim_number, .before = everything())
    sim_results =
      sim_results |>
      bind_rows(current_results)
```

```
}
  return(sim_results)
sim_results = do_n_sims(
 n_sims = 100,
 mu = mean(glucose_data),
  sigma2 = var(glucose_data),
  n = 100 # this is the number of samples per simulated data set
sim_results |> head(10)
#> # A tibble: 10 x 10
#>
      sim_number `mu-hat` `sigma-hat` se_hat confint_left confint_right tstat
#>
           <int>
                    <dbl>
                                 <dbl> <dbl>
                                                     <dbl>
                                                                    <dbl> <dbl>
#>
   1
               1
                     99.8
                                  9.24 0.924
                                                      97.9
                                                                    102. 11.9
   2
               2
                     98.3
                                11.9
                                        1.19
                                                      96.0
                                                                    101.
                                                                           8.00
#>
   3
               3
                     98.8
                                 8.81 0.881
                                                      97.0
                                                                    101.
                                                                          11.3
#>
   4
               4
                                  9.40 0.940
                                                                          11.6
#>
                     99.7
                                                      97.8
                                                                    102.
   5
               5
                     99.0
                                  9.72 0.972
                                                      97.1
                                                                    101.
                                                                          10.5
#>
   6
               6
                     98.6
                                10.6
                                        1.06
                                                      96.4
                                                                    101.
                                                                           9.18
               7
                                                                    102. 11.5
#>
   7
                    100.
                                  9.86 0.986
                                                      98.1
#>
   8
               8
                     97.7
                                 11.1
                                                      95.5
                                                                     99.9 8.03
                                        1.11
#>
   9
               9
                     98.1
                                  9.86 0.986
                                                      96.2
                                                                    100.
                                                                           9.45
                     97.3
                                  9.68 0.968
#> 10
              10
                                                      95.3
                                                                     99.2 8.74
#> # i 3 more variables: pval <dbl>, `confint covers true mu` <lgl>,
       `test rejects null hypothesis` <lgl>
```

The simulation results are in! Now we have to analyze them.

C.4.7.3. Analyze simulation results

To do that, we write another function:

```
summarize_sim = function(
    sim_results,
    mu = mean(glucose_data),
    sigma2 = var(glucose_data),
    n = 100)
  # calculate the true standard error based on the data-generating parameters:
  `se(mu-hat)` = sqrt(sigma2/n)
  sim_results |>
    summarize(
      `bias[mu-hat]` = mean(`mu-hat`) - mu,
      `SE(mu-hat)` = sd(`mu-hat`),
      `bias[SE-hat]` = mean(se_hat) - `se(mu-hat)`,
      `SE(SE-hat)` = sd(se_hat),
      coverage = mean(`confint covers true mu`),
      power = mean(`test rejects null hypothesis`)
}
```

Let's try it out:

```
sim_summary = summarize_sim(
   sim_results,
   mu = mean(glucose_data),
```

```
# this function needs to know the true parameter values in order to assess bias
  sigma2 = var(glucose_data),
 n = 100)
sim_summary
#> # A tibble: 1 x 6
     `bias[mu-hat]` `SE(mu-hat)` `bias[SE-hat]` `SE(SE-hat)` coverage power
#>
              <dbl>
                           <dbl>
                                           <dbl>
                                                        <dbl>
                                                                  <dbl> <dbl>
#> 1
            -0.0334
                           0.999
                                        -0.00826
                                                       0.0752
                                                                   0.98
```

From this simulation, we observe that our estimate of μ , $\hat{\mu}$, has minimal bias, and so does our estimate of $SE(\hat{\mu})$, $\hat{SE}(\hat{\mu})$.

The confidence intervals captured the true value even more often than they were supposed to, and the hypothesis test always rejected the null hypothesis.

I wonder what would happen with a different sample size, a different true μ value, or a different σ^2 value...

D. Common Mistakes

Configuring R

Functions from these packages will be used throughout this document:

```
library(conflicted) # check for conflicting function definitions
# library(printr) # inserts help-file output into markdown output
library(rmarkdown) # Convert R Markdown documents into a variety of formats.
library(pander) # format tables for markdown
library(ggplot2) # graphics
library(ggeasy) # help with graphics
library(ggfortify) # help with graphics
library(dplyr) # manipulate data
library(tibble) # `tibble`s extend `data.frame`s
library(magrittr) # `%>%` and other additional piping tools
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(haven) # import Stata files
```

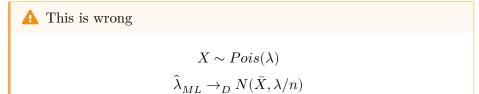
D. Common Mistakes

```
library(latex2exp) # use LaTeX in R code (for figures and tables)
library(fs) # filesystem path manipulations
library(survival) # survival analysis
library(survminer) # survival analysis graphics
library(KMsurv) # datasets from Klein and Moeschberger
library(parameters) # format model output tables for
library(webshot2) # convert interactive content to static for pdf
library(forcats) # functions for categorical variables ("factors")
library(stringr) # functions for dealing with strings
library(lubridate) # functions for dealing with dates and times
```

Here are some R settings I use in this document:

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 Σ and E. Really, we should use μ instead of E.

D.2. Quarto

D.2.1.

Make sure not to put a div ::: on the next line after a slide break ---:

--::: notes

There needs to be an empty line between them:

D. Common Mistakes

::: notes :::

D.2.2. library(printr) currently breaks df-print: paged

See https://github.com/yihui/printr/issues/41

E. Notation

Table E.1.: Notation used in this book

symbol	meaning	LaTeX
$\overline{}$	not	\neg
\forall	all	\forall
∃	some	\exists
U	union, "or"	\cup
\cap	intersection, "and"	\cap
	given, conditional on	\mid,
\sum	sum	\sum
Π	$\operatorname{product}$	\prod
μ^-	mean	\mu
$\mathbb{E}[X]$	expectation of X	\mathbb{E}[X]

E.1. The percent sign

The percent sign "%" is just a shorthand for " $\times \frac{1}{100}$ ". The word "percent" comes from the Latin "per centum"; "centum" means 100 in Latin, so "percent" means "per hundred" (c.f., https://en.wikipedia.org/wiki/Percentage)

So, contrary to what you may have learned previously, 10% = 0.1 is a true and correct equality.

E. Notation

Proof.

$$10\% = 10 \times \frac{1}{100}$$
$$= \frac{10}{100}$$
$$= 0.1$$

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)
- Translations from SAS: Kleinman and Horton (2009)

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.1.1. Methods versus functions

See https://adv-r.hadley.nz/oo.html#oop-systems

F.1.2. Debugging R and C code

See https://www.maths.ed.ac.uk/~swood34/RCdebug/RCdebug.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/

These packages are being actively developed by Hadley Wickham¹ and his colleagues at posit²³.

Details:

- Wickham et al. (2019)
- Wickham, Çetinkaya-Rundel, and Grolemund (2023)
- Kuhn and Silge (2022)

F.3. Piping

See Wickham, Çetinkaya-Rundel, and Grolemund $(2023)^5$ for details.

There are currently (2024) two commonly-used pipe operators in R:

- %>%: the "magrittr pipe", from the magrittr 6 package (Bache and Wickham (2022); re-exported 7 by dplyr 8 and others).
- >: the "native pipe", from base R (4.1.0)

¹https://hadley.nz/

²https://posit.co/

³the company formerly known as RStudio⁴

⁵https://r4ds.hadley.nz/data-transform.html#sec-the-pipe

⁶https://cran.r-project.org/web/packages/magrittr/index.html

⁷https://r-pkgs.org/dependencies-in-practice.html#re-exporting

⁸https://cran.r-project.org/web/packages/dplyr/index.html

F.3.1. Which pipe should I use?

Wickham, Çetinkaya-Rundel, and Grolemund (2023) recommends the native pipe⁹:

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

 $^{^9} https://r4ds.hadley.nz/data-transform.html#sec-the-pipe:~:text=So%20why%20do%20we%20recommend%20the%20base%20pipe%3F$

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.

- https://r-pkgs.org/introduction.html#:~:text=This%20book%20espouses,of%20package%20str
- 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 details¹¹

 $^{^{10} \}rm https://survey.stackoverflow.co/2022/\#section-version-control-version-control-systems$

 $^{^{11} \}rm https://r\text{-}pkgs.org/software\text{-}development\text{-}practices.html}\#sec\text{-}sw\text{-}dev\text{-}practices\text{-}git-github}$

F. Statistical computing in R

- https://happygitwithr.com/
- $\bullet \ \ https://usethis.r-lib.org/articles/pr-functions.html$

F.7. Spatial data science

 $\bullet\,$ Pebesma and Bivand (2023)

F.8. Shiny apps

• Read this first: Wickham (2021)

• Use this as a reference: Fay et al. (2021)

G. Contributing to rme

This section outlines how to propose a change to rme. For a detailed discussion on contributing to this and other projects, please see the Tidyverse development contributing guide¹ and the Tidyverse code review principles². This project is not part of the tidyverse, but we have borrowed their development processes.

G.1. Fixing typos

You can fix typos, spelling mistakes, or grammatical errors directly using the GitHub web interface by making changes in the corresponding *source* file. This generally means you'll need to edit a .qmd file. This book is written using Quarto³.

G.2. Bigger changes

If you want to make a bigger change, it's a good idea to first file an issue and make sure someone from the development team agrees that it's needed.

¹https://rstd.io/tidy-contrib

²https://code-review.tidyverse.org/

³https://quarto.org/docs/books/

G.2.1. Pull request⁴ process

- Fork the package and clone onto your computer. If you haven't done this before, we recommend using usethis::create_from_github("d-morrison/rme", fork = TRUE).
- Install all development dependencies with devtools::install_dev_deps(). Make sure you can build the book by running quarto render in a Terminal.
- Create a Git branch for your pull request (PR). We recommend using usethis::pr_init("brief-description-of-change"). Details at https://usethis.r-lib.org/articles/pr-functions.html
- Make your changes, commit to git, and then create a PR by running usethis::pr_push(), and following the prompts in your browser.
 The title of your PR should briefly describe the change. The body of your PR should contain Fixes #issue-number.
- Add a bullet to the top of NEWS.md (i.e. just below the first header). Follow the style described in https://style.tidyverse.org/news.html.

G.2.2. Code style

• New code should follow the tidyverse style guide⁵. You can use the styler⁶ package to apply these styles, but please don't restyle code that has nothing to do with your PR.

⁴https://usethis.r-lib.org/articles/pr-functions.html#whats-a-pull-request

⁵https://style.tidyverse.org

⁶https://CRAN.R-project.org/package=styler

G.3. Code of Conduct

Please note that the rme project is released with a Contributor Code of Conduct⁷. By contributing to this project you agree to abide by its terms.

⁷CODE_OF_CONDUCT.md

Index

estimand, 420 estimate, 421 estimated value, 421 estimator, 421 expectation, 414 expected value, 414