Regression Models for Epidemiology

Ezra Morrison

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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 Rocke[1]'s materials from the 2021 edition of this course[2]
- Hua Zhou[3]'s materials from the 2020 edition of Biostat 200C at UCLA[4]
- Vittinghoff et al. (2012)
- Dobson and Barnett (2018)
- Harrell (2015)

> **! Important**
>
> I do not claim any of this content as my own original intellectual work. I have attempted to provide more detailed disclaimers for specific sections that are heavily derivative of, or even copied directly from, external sources.
> Please see also the list of contributors on GitHub: https://github.com/d-morrison/rme/graphs/contributors

Using these lecture notes

These lecture notes are available online at https://d-morrison.github.io/rme/. The online notes are searchable and are currently being iteratively updated[5]. A pdf version of the notes is also downloadable from https://d-morrison.github.io/rme/Regression-Models-for-Epidemiology.pdf, and the source files are available at https://github.com/d-morrison/rme.

Compiling chapters as lecture slide decks

Each chapter's source file can also be compiled as a lecture slide deck, using the `_quarto-revealjs.yml`[6] Quarto profile[7] included in the git repository on Github[8].

For example, to compile Chapter 3 as a slide deck:

[1] https://dmrocke.ucdavis.edu/
[2] https://dmrocke.ucdavis.edu/Class/EPI204-Spring-2021/EPI204-Spring-2021.html
[3] https://hua-zhou.github.io/
[4] https://ucla-biostat-200c-2020spring.github.io/schedule/schedule.html
[5] see the source file repository for recent changes: https://github.com/d-morrison/rme
[6] https://github.com/d-morrison/rme/blob/main/_quarto-revealjs.yml
[7] https://quarto.org/docs/projects/profiles.html
[8] https://github.com/d-morrison/rme

1) install quarto[9]
2) clone the project repository from Github[10]
3) Install the project dependencies using `devtools`:

```
library(devtools) # install from CRAN if needed
devtools::install_deps()
```

4) Render the chapter using the `revealjs` profile using the following terminal shell command:

```
quarto render logistic-regression.qmd --profile=revealjs
```

You can also render all the chapters listed in the `_quarto-revealjs.yml`[11] Quarto profile[12] as slide decks simultaneously:

```
quarto render --profile=revealjs
```

Extracting LaTeX commands from the online version of the notes

If you want to extract the LaTeX commands for any math expressions in the online lecture notes, you should be able to right-click and get this pop-up menu:

Figure 1.: Pop-up menu produced by right-clicking on math in online notes

If you select "TeX commands", you will get a window with LaTeX code.[13]

[9] https://quarto.org/docs/get-started/
[10] https://github.com/d-morrison/rme
[11] https://github.com/d-morrison/rme/blob/main/_quarto-revealjs.yml
[12] https://quarto.org/docs/projects/profiles.html
[13] MathJax[14] is more or less a dialect of LaTeX

Figure 2.: LaTeX source code window

You can also grab the TeX commands from the quarto source files on github, but those files use custom macros (defined in https://github.com/d-morrison/rme/blob/main/macros.qmd), so it's a little harder to reuse code from the source files.

Dark Mode

The online notes have two color palette themes: light and dark. You can toggle between them using the oval button near the top-left corner:

Figure 3.: Palette toggle

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 I encourage you 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 that I've come across; I haven't had time to read some of them thoroughly yet, but they're all on my to-do list. I'll add my thoughts on them over time.

- Dobson and Barnett (2018) is a classic textbook on GLMs. It was used in UCLA Biostatistics's MS-level GLMs course (Biostat 200C) when I took it, and it helped me a lot. It is fairly mathematically rigorous and concise, bordering on terse. It covers GLMs in detail, and survival analysis briefly, and it also has helpful chapters on Bayesian methods. I have adapted examples and explanations from it extensively in these notes.
- Wakefield (2013) covers GLMs and hierarchical models using both Bayesian and frequentist inference;
  - statistics PhD level
  - author: UW biostatistics professor Jon Wakefield[15]
  - used in UCLA Biostat 250C[16]
- Hosmer, Lemeshow, and Sturdivant (2013) is a classic text on logistic regression. I haven't read it yet.
- Agresti (2012) is another classic text for GLMs. I haven't read it yet.
- Agresti (2018) appears to be a more applied version of Agresti (2012). I haven't read it yet. There are extra exercises[17] and other resources available on the Student Companion Site[18]
- Agresti (2015) has "More than 400 exercises for readers to practice and extend the theory, methods, and data analysis"; might be more theoretical?
- Agresti (2010) is specifically about ordinal data.
- Dunn and Smyth (2018) is a recent textbook on GLMs. It doesn't cover time-to-event models, and it doesn't use the modern `tidyverse`[19] packages (`ggplot2`[20], `dplyr`[21], etc.), but otherwise it seems great. Edelmann (2019) reviews this book formally.
- Moore (2016) is a recent textbook on survival analysis. It also doesn't use the `tidyverse`, but otherwise seems great.

[15] https://www.biostat.washington.edu/people/jon-wakefield
[16] https://donatello-telesca.com/biostatistics-251-
[17] https://bcs.wiley.com/he-bcs/Books?action=resource&bcsId=11293&itemId=1119405262&resourceId=44770
[18] https://bcs.wiley.com/he-bcs/Books?action=index&itemId=1119405262&bcsId=11293
[19] https://tidyverse.org/
[20] https://ggplot2.tidyverse.org/
[21] https://dplyr.tidyverse.org/

- Klein and Moeschberger (2003) is a classic text for survival analysis. I read most of it in grad school, and it was very helpful. Examples and explanations from it are borrowed extensively in the second half of these notes (partially filtered through David Rocke's course notes.)
- Kalbfleisch and Prentice (2011) is another classic survival analysis text; I haven't read it yet.
- David G. Kleinbaum and Klein (2010) is a mostly applied-level "self-learning" text for logistic regression; I read it cover-to-cover before grad school, and found it very helpful.
- David G. Kleinbaum and Klein (2012) is the corresponding "self-learning" text for survival analysis; I read it cover-to-cover before grad school, and found it very helpful.
- David G. Kleinbaum, Kupper, and Morgenstern (1982), by the same authors, has a solutions manual (David G. Kleinbaum, Kupper, and Morgenstern (1983))
- David G. Kleinbaum et al. (2014) is also by the same group, in a similar style
- Harrell (2015) is another popular textbook. It uses `ggplot2`[22] but not `dplyr`[23], and covers logistic regression and survival analysis (no Poisson or NB models?). An abbreviated but continuously updated version with audio clips is available at https://hbiostat.org/rmsc/.
- Fox (2015) is another standard text. [24]
- McCullagh and Nelder (1989) is a classic, theoretical textbook on GLMs [25]
- 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. The authors are UCSF professors, and it is used for the core Epi PhD courses there. I read this book nearly cover-to-cover before grad school, and it was hugely helpful for me, both for statistical modeling and for causal inference (I think it provided my first exposure to DAGs).
- McCulloch, Searle, and Neuhaus (2008) is also by UCSF professors
- Faraway (2016) has GLMs but not survival analysis
- Selvin (2001) provides worked-out examples of applications for a wide range of statistical analysis techniques. The Author[26] is a retired UC Berkeley Biostatistics professor; he used it in a graduate-level biostat/epi course.
- Selvin (2004) is by the same author
  - recommended by Jewell (2003) for Poisson regression
- Jewell (2003) is by another UC Berkeley professor[27]; it mostly covers logistic regression, with one chapter on survival analysis.

[22] https://ggplot2.tidyverse.org/
[23] https://dplyr.tidyverse.org/
[24] I don't have anything to say about this book, because I haven't opened it yet, but I've heard it's great!
[25] haven't opened it either
[26] https://publichealth.berkeley.edu/people/steve-selvin
[27] https://publichealth.berkeley.edu/people/nicholas-jewell

- https://ucla-biostat-200c-2020spring.github.io/schedule/schedule.html provides course notes for "Biostat 200C - Methods in Biostatistics C" at UCLA, which is at the Biostatistics MS level.
- 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 (2024) is currently in-development
- Clayton and Hills (2013) covers binary regression, count regression, and survival analysis. Haven't started it yet.
- https://thomaselove.github.io/2020-432-book/index.html is another set of lecture notes.
- Woodward (2013) covers GLMs and survival; haven't read it yet, but it looks comprehensive.
- Roback and Legler (2021) is recent and uses the `tidyverse`; doesn't appear to cover survival analysis.
- Wood (2017) is about generalized *additive* models but includes a detailed summary of GLMs.
- Kutoyants (2023) appears to be a complete book on Poisson models.
- Hardin and Hilbe (2018) uses Stata.
- Andrews and Herzberg (2012) is a classic "learn-by-example" book with many datasets amenable to GLMs
- Cannell and Livingston (2024) is another open-source, online textbook like this one; it is primarily about statistical programming, but it includes full chapters on linear regression[28], logistic regression[29], and Poisson regression[30]. There is currently (2024/06) a placeholder chapter for survival analysis[31].
- Gelman and Hill (2007) covers GLMs as well as hierarchical extensions of GLMs. No survival models?
- In-development new Gelman et al book: https://bookdown.org/jl5522/MRP-case-studies/
- Soch (2023) is a collection of proofs for results in probability, statistics, and related computational sciences.
- Suárez et al. (2017) covers GLMs but not survival analysis
- Greenland (2014) is a lengthy chapter from the Handbook of Epidemiology
- Rothman et al. (2021) contains several chapters on regression analyses in epidemiology
- Rawlings, Pantula, and Dickey (1998) is used in PLS 206[32]

[28] https://www.r4epi.com/linear-regression
[29] https://www.r4epi.com/linear-regression-1
[30] https://www.r4epi.com/poisson-regression
[31] https://www.r4epi.com/cox-proportional-hazards-regression
[32] https://catalog.ucdavis.edu/search/?q=PLS+206

- Bolker (2008) is used in PLS 207[33]
- Ken Rice[34]'s slides from Stat/Biostat 570 at University of Washington are also useful: https://drive.google.com/file/d/1VwosGvHtRtKnC7P3ja7RAUawvvudgc9T/view

Other similar courses at UC Davis:

- MPM 202[35], 203[36], 204[37] "Medical Statistics I-III"
- PHR 266/SPH 266[38] "Applied Analytic Epidemiology"
  - covers similar content; that course was designed for professional Master's students (e.g., MPVM, MPH) and does not assume a knowledge of mathematical statistics.
- PLS 206[39] "Applied Multivariate Modeling in Agricultural & Environmental Sciences"
- STA 101[40] "Advanced Applied Statistics for the Biological Sciences"
- STA 138[41] "Analysis of Categorical Data"
  - emphasizes methods for analyzing categorical outcomes and predictors (i.e. contingency tables).
- STA 207[42] "Statistical Methods for Research II"

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This book is licensed to you under Creative Commons Attribution-NonCommercial-NoDerivatives 4.0 International License[43].

The code samples in this book are licensed under Creative Commons CC0 1.0 Universal (CC0 1.0)[44], i.e. public domain.

[33] https://catalog.ucdavis.edu/search/?q=PLS+207
[34] https://www.biostat.washington.edu/people/ken-rice
[35] https://catalog.ucdavis.edu/search/?q=MPM+202
[36] https://catalog.ucdavis.edu/search/?q=MPM+203
[37] https://catalog.ucdavis.edu/search/?q=MPM+204
[38] https://catalog.ucdavis.edu/search/?q=PHR+266
[39] https://catalog.ucdavis.edu/search/?q=PLS+206
[40] https://catalog.ucdavis.edu/search/?q=STA+101
[41] https://catalog.ucdavis.edu/search/?q=STA+138
[42] https://catalog.ucdavis.edu/search/?q=STA+207
[43] http://creativecommons.org/licenses/by-nc-nd/4.0/
[44] https://creativecommons.org/publicdomain/zero/1.0/

1. Introduction

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(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' = 6)

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 default
legend_text_size = 9
run_graphs = TRUE
```

1.1. Welcome

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

Epi 204 is a course on **regression modeling**.

1.2. What you should already know

> ⚠ Warning
>
> Epi 202, Epi 203, and Sta 108 are prerequisites for this course. If you haven't passed one of these courses, talk to me ASAP.

1.2.1. Epi 202: probability models

- Probability distributions
  - binomial
  - Poisson
  - Gaussian
  - exponential

- Characteristics of probability distributions
  - Mean, median, mode, quantiles
  - Variance, standard deviation, overdispersion

- Characteristics of samples
  - independence, dependence, covariance, correlation
  - ranks, order statistics
  - identical vs nonidentical distribution (homogeneity vs heterogeneity)
  - Laws of Large Numbers
  - Central Limit Theorem for the mean of an iid sample

1.2.2. 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
  - nonparametric tests:
    - Wilcoxon signed-rank test for matched pairs
    - Mann–Whitney/Kruskal-Wallis rank sum test for ≥ 2 independent samples
    - Fisher's exact test for contingency tables
    - Cochran–Mantel–Haenszel-Cox log-rank test

For all of the quantities above, and especially for confidence intervals and p-values, you should know how **both**:

- how to compute them
- how to interpret them

1.2.3. Stat 108: linear regression models

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

1.3. 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

We will start where Epi 203 left off: with linear regression models.

1.4. Motivations for regression models

Exercise 1.1. Why do we need regression models?

Solution 1.1.

- when there's not enough data to analyze every subgroup of interest individually
- especially when subgroups are defined using continuous predictors

[1] https://r4ds.hadley.nz/quarto

1.4.1. Example: Adelie penguins

Figure 1.1.: Palmer penguins

1.4.2. Linear regression

```
ggpenguins2 <-
  ggpenguins +
  stat_smooth(
    method = "lm",
    formula = y ~ x,
    geom = "smooth"
  )

ggpenguins2 |> print()
```

Figure 1.2.: Palmer penguins with linear regression fit

1.4.3. 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

1.4.4. Multiple regression

```
ggpenguins <-
  palmerpenguins::penguins |>
  ggplot(
    aes(
      x = bill_length_mm,
      y = body_mass_g,
      color = species
    )
  ) +
  geom_point() +
  stat_smooth(
    method = "lm",
    formula = y ~ x,
    geom = "smooth"
  ) +
  xlab("Bill length (mm)") +
  ylab("Body mass (g)")
ggpenguins |> print()
```

Figure 1.4.: Palmer penguins - multiple groups

1.4.5. 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)

1.4.6. 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)

1.4.7. Zoom out

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

1.4.8. 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)

1.4.9. Logistic regression

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

f <- function(x) {
  glm1 |>
    predict(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)

1.5. Structure of regression models

Exercise 1.2. What is a regression model?

Definition 1.1 (Regression model)**.** Regression models are conditional probability distribution models:

$$\mathrm{P}(Y|\tilde{X})$$

Exercise 1.3. What are some of the names used for the variables in a regression model $\mathrm{P}(Y|\tilde{X})$?

Definition 1.2 (Outcome)**.** The outcome variable in a regression model is the variable whose distribution is being described; in other words, the variable on the left-hand side of the "|" ("pipe") symbol.

The outcome variable is also called the **response variable**, **regressand**, **predicted variable**, **explained variable**, **experimental variable**, **output variable**, **dependent variable**, **endogenous variables**, **target**, or **label**.

and is typically denoted Y.

Definition 1.3 (Predictors)**.** The predictor variables in a regression model are the conditioning variables defining subpopulations among which the outcome distribution might vary.

Predictors are also called **regressors**, **covariates**, **independent variables**, **explanatory variables**, **risk factors**, **exposure variables**, **input variables**, **exogenous variables**, **candidate variables** (Dunn and Smyth (2018)), **carriers** (Dunn and Smyth (2018)), **manipulated variables**, or **features** and are typically denoted $\tilde{X}$. [2]

Table 1.1.: Common pairings of terms for variables $\tilde{X}$ and Y in regression models $P(Y|\tilde{X})$ [4]

$\tilde{X}$	Y	usual context
input	output	
independent	dependent	
predictor	predicted or response	
explanatory	explained	
exogenous	endogenous	econometrics
manipulated	measured	randomized controlled experiments
exposure	outcome	epidemiology
feature	label or target	machine learning

Exercise 1.4. What is the general structure of a generalized linear model?

[2] The "~" ("tilde") symbol in the notation $\tilde{X}$ indicates that $\tilde{X}$ is a vector. See the appendices[3] for a table of notation used in these notes.

[4] adapted from https://en.wikipedia.org/wiki/Dependent_and_independent_variables#Synonyms

---

Solution 1.2. Generalized linear models have three components:

1. The **outcome distribution** family: $\mathrm{p}(Y|\mu(\tilde{x}))$
2. The **link function**: $g(\mu(\tilde{x})) = \eta(\tilde{x})$
3. The **linear component**: $\eta(\tilde{x}) = \tilde{x} \cdot \beta$

---

1. The **outcome distribution** family (a.k.a. the **random component** of the model)

- Gaussian (normal)
- Binomial
- Poisson
- Exponential
- Gamma
- Negative binomial

---

2. The **linear component** (a.k.a. the *linear predictor* or *linear functional form*) describing how the covariates combine to define subpopulations:

$$\eta(\tilde{x}) \stackrel{\text{def}}{=} \tilde{x}^\top \tilde{\beta} = \beta_0 + \beta_1 x_1 + \beta_2 x_2 + ...$$

---

3. The **link function** relating the outcome distribution to the linear component, typically through the mean:

- identity: $\mu(y) = \eta(\tilde{x})$
- logit: $\log\left\{\frac{\mu(y)}{1-\mu(y)}\right\} = \eta(\tilde{x})$
- log: $\log\{\mu(y)\} = \eta(\tilde{x})$
- inverse: $(\mu(y))^{-1} = \eta(\tilde{x})$
- clog-log: $\log\{-\log\{1-\mu(y)\}\} = \eta(\tilde{x})$

Components 2 and 3 together are sometimes called the **systematic component** of the model (for example, in Dunn and Smyth (2018)).

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 βx. 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 1.2.: 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

Family	Links
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 1.3.: R `glm()` Link Functions; $\eta = X\beta = g(\mu)$

Name	Domain	Range	Link Function	Inverse Link Function
identity	$(-\infty, \infty)$	$(-\infty, \infty)$	$\eta = \mu.$	$\mu = \eta$
log	$(0, \infty)$	$(-\infty, \infty)$	$\eta = \log \mu$	$\mu = \exp\{\eta\}$
inverse	$(0, \infty)$	$(0, \infty)$	$\eta = 1/\mu$	$\mu = 1/\eta$
logit	$(0, 1)$	$(-\infty, \infty)$	$\eta = \log \mu/(1-\mu)$	$\mu = \exp\{\eta\}/(1+\exp\{\eta\})$
probit	$(0, 1)$	$(-\infty, \infty)$	$\eta = \Phi^{-1}(\mu)$	$\mu = \Phi(\eta)$
cloglog	$(0, 1)$	$(-\infty, \infty)$	$\eta = \log - \log 1 - \mu$	$\mu = 1 - \exp\{-\exp\{\eta\}\}$
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(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' = 6)

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 default
legend_text_size = 9
run_graphs = TRUE
```

```
include_reference_lines <- FALSE
```

Note

This content is adapted from:

- Dobson and Barnett (2018), Chapters 2-6
- Dunn and Smyth (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 and UC Davis STA 108.
- David G. Kleinbaum et al. (2014): same first author as David G. Kleinbaum and Klein (2010) and David G. Kleinbaum and Klein (2012)
- *Linear Models with R* (Faraway 2025)
- *Applied Linear Regression* by Sanford Weisberg (Weisberg 2005)

For more recommendations, see the discussion on Reddit[a].

- see also https://web.stanford.edu/class/stats191 [1]

[a] https://www.reddit.com/r/statistics/comments/qwgctl/q_books_on_applied_linear_modelsregression_for/

[1] the current version of the first regression course I ever took

2.1. Overview

2.1.1. Why this course includes linear regression

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

2.1.2. Chapter overview

- Section 2.2: how to interpret linear regression models
- Section 2.3: how to estimate linear regression models
- Section 2.4: how to quantify uncertainty about our estimates
- Section 2.8: how to tell if your model is insufficiently complex

2.2. Understanding Gaussian Linear Regression Models

2.2.1. Motivating example: birthweights and gestational age

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

2.2.2. Dobson `birthweight` data

2.2.2.1. Data as table

2.2.2.2. Reshape data for graphing

2.2.2.3. Data as graph

```
plot1 <- bw |>
  ggplot(aes(
    x = age,
    y = weight,
    shape = sex,
    col = sex
  )) +
```

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

```
library(dobson)
data("birthweight", package = "dobson")
birthweight
#> # A tibble: 12 x 4
#>    `boys gestational age` `boys weight` `girls gestational age` `girls weight`
#>                     <dbl>         <dbl>                   <dbl>          <dbl>
#>  1                     40          2968                      40           3317
#>  2                     38          2795                      36           2729
#>  3                     40          3163                      40           2935
#>  4                     35          2925                      38           2754
#>  5                     36          2625                      42           3210
#>  6                     37          2847                      39           2817
#>  7                     41          3292                      40           3126
#>  8                     40          3473                      37           2539
#>  9                     37          2628                      36           2412
#> 10                     38          3176                      38           2991
#> 11                     40          3421                      39           2875
#> 12                     38          2975                      40           3231
```

```
  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))
```

Table 2.2.: `birthweight` data reshaped

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

bw
#> # A tibble: 24 x 6
#>    sex      age weight    id male  female
#>    <fct>  <dbl>  <dbl> <int> <lgl> <lgl>
#>  1 male      40   2968     1 TRUE  FALSE
#>  2 female    40   3317     2 FALSE TRUE
#>  3 male      38   2795     3 TRUE  FALSE
#>  4 female    36   2729     4 FALSE TRUE
#>  5 male      40   3163     5 TRUE  FALSE
#>  6 female    40   2935     6 FALSE TRUE
#>  7 male      35   2925     7 TRUE  FALSE
#>  8 female    38   2754     8 FALSE TRUE
#>  9 male      36   2625     9 TRUE  FALSE
#> 10 female    42   3210    10 FALSE TRUE
#> # i 14 more rows
```

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

2.2.2.4. Data notation

Let's define some notation to represent this data:

- Y: birthweight (measured in grams)
- S: chromosomal sex: "male" (XY) or "female" (XX)
- M: indicator variable for $S =$ "male"[2]
- $M = 0$ if $S =$ "female"
- $M = 1$ if $S =$ "male"
- F: indicator variable for $S =$ "female"[3]
- $F = 1$ if $S =$ "female"
- $F = 0$ if $S =$ "male"
- A: estimated gestational age at birth (measured in weeks).

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.

M and F are called **dummy variables**; together, they are a numeric representation of the categorical variable S. Dummy variables with values 0 and 1 are also called **indicator**

[2] M is implicitly a deterministic function of S
[3] F is implicitly a deterministic function of S

variables. There are other ways to construct dummy variables, such as using the values -1 and 1 (see Dobson and Barnett (2018) §2.4 for details).

2.2.3. Parallel lines regression

(c.f. Dunn and Smyth (2018) §2.10.3[4])

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

$$\begin{aligned} Y|M, A &\sim_{\text{ciid}} N(\mu(M, A), \sigma^2) \\ \mu(m, a) &= \beta_0 + \beta_M m + \beta_A a \end{aligned} \tag{2.1}$$

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
)

library(parameters)
bw_lm1 |>
  parameters::parameters() |>
  parameters::print_md(
    include_reference = include_reference_lines,
    select = "{estimate}"
  )
```

Table 2.3.: Regression parameter estimates for Model 2.1 of `birthweight` data

Parameter	Coefficient
(Intercept)	-1773.32
sex (male)	163.04
age	120.89

[4] https://link.springer.com/chapter/10.1007/978-1-4419-0118-7_2#Sec31

```
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.: Graph of Model 2.1 for `birthweight` data

2.2.3.1. Model assumptions and predictions

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

Exercise 2.1. What's the mean birthweight for a female born at 36 weeks?

Table 2.4.: Estimated coefficients for model 2.1

Parameter	Coefficient
(Intercept)	-1773.32
sex (male)	163.04
age	120.89

Solution.

Table 2.5.: Estimated coefficients for model 2.1

Parameter	Coefficient
(Intercept)	-1773.32
sex (male)	163.04
age	120.89

```
pred_female <- coef(bw_lm1)["(Intercept)"] + coef(bw_lm1)["age"] * 36
### or using built-in prediction:
pred_female_alt <- predict(bw_lm1, newdata = tibble(sex = "female", age = 36))
```

$$\begin{aligned} E[Y|M=0, A=36] &= \beta_0 + (\beta_M \cdot 0) + (\beta_A \cdot 36) \\ &= -1773.321839 + (163.039303 \cdot 0) + (120.894327 \cdot 36) \\ &= 2578.873934 \end{aligned}$$

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

Table 2.6.: Estimated coefficients for model 2.1

Parameter	Coefficient
(Intercept)	-1773.32
sex (male)	163.04
age	120.89

Solution.

Table 2.7.: Estimated coefficients for model 2.1

Parameter	Coefficient
(Intercept)	-1773.32
sex (male)	163.04
age	120.89

```
pred_male <-
  coef(bw_lm1)["(Intercept)"] +
  coef(bw_lm1)["sexmale"] +
  coef(bw_lm1)["age"] * 36
```

$$
\begin{aligned}
E[Y|M=1, A=36] &= \beta_0 + \beta_M \cdot 1 + \beta_A \cdot 36 \\
&= 2741.913237
\end{aligned}
$$

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
#>   -1773.322     163.039     120.894
```

Solution.

$$
\begin{aligned}
&E[Y|M=1, A=36] - E[Y|M=0, A=36] \\
&= 2741.913237 - 2578.873934 \\
&= 163.039303
\end{aligned}
$$

Shortcut:

$$
\begin{aligned}
&E[Y|M=1, A=36] - E[Y|M=0, A=36] \\
&= (\beta_0 + \beta_M \cdot 1 + \beta_A \cdot 36) - (\beta_0 + \beta_M \cdot 0 + \beta_A \cdot 36) \\
&= \beta_M \\
&= 163.039303
\end{aligned}
$$

Age cancels out 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.

This characteristic is an assumption of the model specified by Equation 2.1. It's hardwired into the parametric model structure, even before we estimated values for those parameters.

2.2.3.2. Coefficient Interpretation

Recall Model 2.1:

$$
E[Y|M=m, A=a] = \mu(m,a) = \beta_0 + \beta_M m + \beta_A a
$$

Slope (of the mean with respect to age) for males:

$$
\begin{aligned}
\frac{d}{da}\mu(1,a) &= \frac{d}{da}(\beta_0 + \beta_M 1 + \beta_A a) \\
&= \left(\frac{d}{da}\beta_0 + \frac{d}{da}\beta_M 1 + \frac{d}{da}\beta_A a\right) \\
&= (0 + 0 + \beta_A) \\
&= \beta_A
\end{aligned}
$$

Slope for females:

$$\begin{aligned}\frac{d}{da}\mu(0,a) &= \frac{d}{da}(\beta_0 + \beta_M 0 + \beta_A a) \\ &= \left(\frac{d}{da}\beta_0 + \frac{d}{da}\beta_M 0 + \frac{d}{da}\beta_A a\right) \\ &= (0 + 0 + \beta_A) \\ &= \beta_A\end{aligned}$$

Exercise 2.4. What is the interpretation of β_A in Model 2.1?

Solution.

$$\begin{aligned}\frac{d}{da}\mu(m,a) &= \frac{d}{da}(\beta_0 + \beta_M m + \beta_A a) \\ &= \left(\frac{d}{da}\beta_0 + \frac{d}{da}\beta_M m + \frac{d}{da}\beta_A a\right) \\ &= (0 + 0 + \beta_A) \\ &= \beta_A\end{aligned}$$

Conclusion:

$$\beta_A = \frac{d}{da}\mu(m,a)$$

β_A is the slope of mean birthweight with respect to gestational age, adjusting for sex.

Or we can plug in the definition of slope:

$$\beta_A = E[Y|M = m, A = a + 1] - E[Y|M = m, A = a]$$

Exchangeability and consistency have not been assessed; so we are not discussing potential outcomes (causality), only observed outcomes.

Exercise 2.5. What is the interpretation of β_M in Model 2.1?

Solution.

More precisely written:

$$\mathrm{E}[Y|M=m, A=a] = \mu(m,a) = \begin{cases} \beta_0 + \beta_M m + \beta_A a, & \text{for } m \in \{0,1\} \\ \text{undefined}, & \text{for } m \notin \{0,1\} \end{cases}$$

The model is undefined for $m \notin \{0,1\}$, so the derivative with respect to m doesn't exist.

$$\begin{aligned} E[Y|M=1, A=a] &= \beta_0 + \beta_M 1 + \beta_A a \\ &= \beta_0 + \beta_M + \beta_A a \\ E[Y|M=0, A=a] &= \beta_0 + \beta_M 0 + \beta_A a \\ &= \beta_0 + \beta_A a \end{aligned}$$

So:

$$\begin{aligned} E[Y|M=1, A=a] - E[Y|M=0, A=a] &= (\beta_0 + \beta_M + \beta_A a) - (\beta_0 + \beta_A a) \\ &= \beta_M \end{aligned}$$

Therefore:

$$\begin{aligned} \beta_M &= E[Y|M=1, A=a] - E[Y|M=0, A=a] \\ &= \mu(1,a) - \mu(0,a) \end{aligned}$$

In words: β_M is the difference in mean birthweight between males and females adjusting for age.

Exercise 2.6. $\beta_0 = ?$

Solution.

$$\begin{aligned} \mathrm{E}[Y|M=0, A=0] &= \mu(0,0) \\ &= \beta_0 + \beta_M 0 + \beta_A 0 \\ &= \beta_0 \\ \beta_0 &= \mathrm{E}[Y|M=0, A=0] = \mu(0,0) \end{aligned}$$

β_0 is the mean birthweight for a female with gestational age 0 weeks.

2.2.4. Interactions

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

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

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

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() |>
  parameters::print_md(
    include_reference = include_reference_lines,
    select = "{estimate}"
  )
```

Table 2.8.: Birthweight model with interaction term

Parameter	Coefficient
(Intercept)	-2141.67
sex (male)	872.99
age	130.40
sex (male) × 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):

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

If you want to understand a coefficient in a model with interactions, collect terms for the corresponding variable, and you will see which other covariates interact with the variable whose coefficient you are interested in. In this case, the association between A (age) varies between males and females (that is, by sex S). [5] 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. 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: each non-interaction slope coefficient is the difference in means per unit difference in its corresponding variable, when all interacting variables are set to 0.

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

Exercise 2.7. According to this model, what's the mean birthweight for a female born at 36 weeks?

Parameter	Coefficient
(Intercept)	-2141.67
sex (male)	872.99
age	130.40
sex (male) × age	-18.42

Solution.

Parameter	Coefficient
(Intercept)	-2141.67
sex (male)	872.99
age	130.40
sex (male) × age	-18.42

[5] some call this kind of variation "interaction" or "effect modification", but "act", "effect", "modify", and "by" all suggest causality, which we are not prepared to assess here; let's try to avoid using causal terms, unless we are constructing a causal model.

```
pred_female <- coef(bw_lm2)["(Intercept)"] + coef(bw_lm2)["age"] * 36
```

$$E[Y|M = 0, X_2 = 36] = \beta_0 + \beta_M \cdot 0 + \beta_A \cdot 36 + \beta_{AM} \cdot (0 * 36) = 2552.733333$$

Exercise 2.8. What's the mean birthweight for a male born at 36 weeks?

Parameter	Coefficient
(Intercept)	-2141.67
sex (male)	872.99
age	130.40
sex (male) × age	-18.42

Solution.

Parameter	Coefficient
(Intercept)	-2141.67
sex (male)	872.99
age	130.40
sex (male) × age	-18.42

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

$$\begin{aligned} E[Y|M = 1, X_2 = 36] &= \beta_0 + \beta_M \cdot 1 + \beta_A \cdot 36 + \beta_{AM} \cdot 1 \cdot 36 \\ &= 2762.706897 \end{aligned}$$

Exercise 2.9. What's the difference in mean birthweights between males born at 36 weeks and females born at 36 weeks?

Solution.

$$
\begin{aligned}
&E[Y|M=1, A=36] - E[Y|M=0, A=36] \\
&= (\beta_0 + \beta_M \cdot 1 + \beta_A \cdot 36 + \beta_{AM} \cdot 1 \cdot 36) \\
&\quad - (\beta_0 + \beta_M \cdot 0 + \beta_A \cdot 36 + \beta_{AM} \cdot 0 \cdot 36) \\
&= \beta_S + \beta_{AM} \cdot 36 \\
&= 209.973563
\end{aligned}
$$

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.

2.2.4.1. Coefficient Interpretation

Exercise 2.10. What is the interpretation of β_M in Model 2.2?

Solution.

Mean birthweight among males with gestational age 0 weeks:

$$
\begin{aligned}
\mu(1,0) &= \mathrm{E}[Y|M=1, A=0] \\
&= \beta_0 + \beta_M \cdot 1 + \beta_A \cdot 0 + \beta_{AM} \cdot 1 \cdot 0 \\
&= \beta_0 + \beta_M
\end{aligned}
$$

Mean birthweight among females with gestational age 0 weeks:

$$
\begin{aligned}
\mu(0,0) &= \mathrm{E}[Y|M=0, A=0] \\
&= \beta_0 + \beta_M \cdot 0 + \beta_A \cdot 0 + \beta_{AM} \cdot 0 \cdot 0 \\
&= \beta_0
\end{aligned}
$$

$$
\begin{aligned}
\beta_M &= \mu(1,0) - \mu(0,0) \\
&= \mathrm{E}[Y|M=1, A=0] - \mathrm{E}[Y|M=0, A=0]
\end{aligned}
$$

β_M is the difference in mean birthweight between males with gestational age 0 weeks and females with gestational age 0 weeks.

Exercise 2.11. What is the interpretation of β_{AM} in Model 2.2?

Solution.

Slope among males:

$$\begin{aligned}\frac{\partial}{\partial a}\mu(1,a) &= \frac{\partial}{\partial a}\left(\beta_0 + \beta_M \cdot 1 + \beta_A \cdot a + \beta_{AM} \cdot 1 \cdot a\right)\\ &= \frac{\partial}{\partial a}\left(\beta_0 + \beta_M + \beta_A \cdot a + \beta_{AM} \cdot a\right)\\ &= \beta_A + \beta_{AM}\end{aligned}$$

or

$$\begin{aligned}E[Y|1,a+1] - E[Y|1,a] =& \beta_0 + \beta_M 1 + \beta_A(a+1) + \beta_{AM}1(a+1)\\ &- (\beta_0 + \beta_M 1 + \beta_A(a) + \beta_{AM}1(a))\\ =& \beta_A + \beta_{AM}\end{aligned}$$

Slope among females:

$$\begin{aligned}\frac{\partial}{\partial a}\mu(0,a) &= \frac{\partial}{\partial a}\left(\beta_0 + \beta_M \cdot 0 + \beta_A \cdot a + \beta_{AM} \cdot 0 \cdot a\right)\\ &= \frac{\partial}{\partial a}\left(\beta_0 + \beta_A \cdot a\right)\\ &= \beta_A\end{aligned}$$

or

$$\begin{aligned}E[Y|0,a+1] - E[Y|0,a] =& \beta_0 + \beta_M 0 + \beta_A(a+1) + \beta_{AM}0(a+1)\\ &- (\beta_0 + \beta_M 0 + \beta_A(a) + \beta_{AM}0(a))\\ =& \beta_0 + \beta_A(a+1) - (\beta_0 + \beta_A(a))\\ =& \beta_A\end{aligned}$$

Difference in slopes:

$$\begin{aligned}\frac{\partial}{\partial a}\mu(1,a) - \frac{\partial}{\partial a}\mu(0,a) &= \beta_A + \beta_{AM} - \beta_A\\ &= \beta_{AM}\end{aligned}$$

or

$$\begin{aligned}(E[Y|1,a+1] - E[Y|1,a]) - (E[Y|0,a+1] - E[Y|0,a]) &= \beta_A + \beta_{AM} - \beta_A\\ &= \beta_{AM}\end{aligned}$$

Therefore

$$\begin{aligned}\beta_{AM} =& \frac{\partial}{\partial a}\mu(1,a) - \frac{\partial}{\partial a}\mu(0,a)\\ =& (E[Y|M=1, A=a+1] - E[Y|M=1, A=a])\\ &- (E[Y|M=0, A=a+1] - E[Y|M=0, A=a])\end{aligned}$$

β_{AM} is the difference in slope of mean birthweight with respect to gestational age between males and females.

2.2.4.2. Compare coefficient interpretations

Table 2.13.: Coefficient interpretations, by model structure

$\mu(m, a)$	$\beta_0 + \beta_M m + \beta_A a$	$\beta_0 + \beta_M m + \beta_A a + \beta_{AM} ma$
β_0	$\mu(0, 0)$	$\mu(0, 0)$
β_A	$\frac{\partial}{\partial a}\mu(m, a)$	$\frac{\partial}{\partial a}\mu(0, a)$
β_M	$\mu(1, a) - \mu(0, a)$	$\mu(1, 0) - \mu(0, 0)$
β_{AM}		$\frac{\partial}{\partial a}\mu(1, a) - \frac{\partial}{\partial a}\mu(0, a)$

In the model with an interaction term multiplying $A \times M$, the interpretation of β_A involves the reference level of M, and interpretation of β_M involves the reference level of A (Table 2.13).

2.2.5. Stratified regression

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

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

Compare this stratified model (Equation 2.3) with our interaction model, Equation 2.2:

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

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 = include_reference_lines,
    select = "{estimate}"
  )
```

Table 2.14.: Birthweight model with interaction term

Parameter	Coefficient
(Intercept)	-2141.67
sex (male)	872.99
age	130.40
sex (male) × age	-18.42

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

```
bw_lm_strat |>
  parameters() |>
  print_md(
    select = "{estimate}"
  )
```

Table 2.15.: Birthweight model - stratified betas

Parameter	Coefficient
sex (female)	-2141.67
sex (male)	-1268.67
sex (female) × age	130.40
sex (male) × age	111.98

2.2.6. 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)

ggbw <-
  bw |>
  ggplot(
    aes(x = age, y = weight)
  ) +
  geom_point() +
  xlab("Gestational Age (weeks)") +
  ylab("Birth Weight (g)")

ggbw2 <- ggbw +
  stat_smooth(
    method = "lm",
    formula = y ~ log(x),
    geom = "smooth"
  ) +
  xlab("Gestational Age (weeks)") +
  ylab("Birth Weight (g)")


ggbw2 |> print()
```

Figure 2.4.: `birthweight` model with `age` entering on log scale

Below is an example with a slightly more obvious curve.

```
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 ~ log(x),
    geom = "smooth"
  ) +
  xlab("Bill length (mm)") +
  ylab("Body mass (g)")


ggpenguins2 |> print()
```

Figure 2.5.: `palmerpenguins` model with `bill_length` entering on log scale

2.3. Estimating Linear Models via Maximum Likelihood

In EPI 203 and our review of MLEs, we learned how to fit outcome-only models of the form $p(X = x|\theta)$ to iid data $\tilde{x} = (x_1, ..., x_n)$ using maximum likelihood estimation.

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

2.3.1. Likelihood

$$
\begin{aligned}
\mathcal{L}_i &\stackrel{\text{def}}{=} p(Y_i = y_i | \tilde{X}_i = \tilde{x}_i) \\
&= (2\pi\sigma^2)^{-1/2} \exp\left\{-\frac{1}{2\sigma^2}\varepsilon_i^2\right\} \\
\varepsilon_i &\stackrel{\text{def}}{=} y_i - \mu_i \\
\mu_i &\stackrel{\text{def}}{=} \mu(x_i) \\
&= x_i \cdot \beta
\end{aligned}
$$

$$
\begin{aligned}
\mathcal{L} &\stackrel{\text{def}}{=} \mathcal{L}(\tilde{y}|\mathbf{x}, \tilde{\beta}, \sigma^2) \\
&\stackrel{\text{def}}{=} \mathrm{p}(\tilde{Y} = \tilde{y}|\mathbf{X} = \mathbf{x}) \\
&= \prod_{i=1}^{n} \mathcal{L}_i
\end{aligned}
\tag{2.4}
$$

2.3.2. Log-likelihood

$$
\begin{aligned}
\ell_i &\stackrel{\text{def}}{=} \log\{\mathcal{L}_i\} \\
&= \log\left\{(2\pi\sigma^2)^{-1/2}\exp\left\{-\frac{1}{2\sigma^2}\varepsilon_i^2\right\}\right\} \\
&= -\frac{1}{2}\log\{2\pi\sigma^2\} - \frac{1}{2\sigma^2}\varepsilon_i^2
\end{aligned}
$$

$$
\begin{aligned}
\ell &\stackrel{\text{def}}{=} \ell(\tilde{y}|\mathbf{x}, \beta, \sigma^2) \\
&\stackrel{\text{def}}{=} \log\{\mathcal{L}(\tilde{y}|\mathbf{x}, \beta, \sigma^2)\} \\
&= \log\left\{\prod_{i=1}^{n}\mathcal{L}_i\right\} \\
&= \sum_{i=1}^{n}\log\{\mathcal{L}_i\} \\
&= \sum_{i=1}^{n}\ell_i \\
&= \sum_{i=1}^{n}\left(-\frac{1}{2}\log\{2\pi\sigma^2\} - \frac{1}{2\sigma^2}\varepsilon_i^2\right) \\
&= -\frac{n}{2}\log\{2\pi\sigma^2\} - \frac{1}{2\sigma^2}\sum_{i=1}^{n}\varepsilon_i^2 \\
&= -\frac{n}{2}\log\{2\pi\sigma^2\} - \frac{1}{2\sigma^2}(\tilde{\varepsilon}\cdot\tilde{\varepsilon}) \\
&= -\frac{n}{2}\log\{2\pi\sigma^2\} - \frac{1}{2\sigma^2}((\tilde{y}-\tilde{\mu})\cdot(\tilde{y}-\tilde{\mu})) \\
&= -\frac{n}{2}\log\{2\pi\sigma^2\} - \frac{1}{2\sigma^2}\big((\tilde{y}-\mathbf{X}\tilde{\beta})\cdot(\tilde{y}-\mathbf{X}\tilde{\beta})\big) \\
&= -\frac{n}{2}\log\{2\pi\sigma^2\} - \frac{1}{2\sigma^2}\sum_{i=1}^{n}\left(y_i - \left(\tilde{x}_i\cdot\tilde{\beta}\right)\right)^2
\end{aligned}
\tag{2.5}
$$

2.3.3. Score function

$$
\begin{aligned}
\mu_i' &\stackrel{\text{def}}{=} \frac{\partial}{\partial\tilde{\beta}}\mu_i \\
&= \frac{\partial}{\partial\tilde{\beta}}\left(\tilde{x}_i\cdot\tilde{\beta}\right) \\
&= \left(\frac{\partial}{\partial\tilde{\beta}}\tilde{\beta}\right)\tilde{x}_i \\
&= \mathbb{I}\tilde{x}_i \\
&= \tilde{x}_i
\end{aligned}
$$

$$
\begin{aligned}
\varepsilon_i' &\stackrel{\text{def}}{=} \frac{\partial}{\partial \tilde{\beta}} \varepsilon_i \\
&= \frac{\partial}{\partial \tilde{\beta}} (y_i - \mu_i) \\
&= \frac{\partial}{\partial \tilde{\beta}} y_i - \frac{\partial}{\partial \tilde{\beta}} \mu_i \\
&= 0 - \tilde{x}_i \\
&= -\tilde{x}_i
\end{aligned}
$$

$$
\begin{aligned}
\ell_i' &\stackrel{\text{def}}{=} \frac{\partial}{\partial \tilde{\beta}} \ell_i \\
&= \frac{\partial}{\partial \tilde{\beta}} \left(-\frac{1}{2} \log\{2\pi\sigma^2\} - \frac{1}{2\sigma^2} \varepsilon_i^2 \right) \\
&= \frac{\partial}{\partial \tilde{\beta}} \left(-\frac{1}{2} \log\{2\pi\sigma^2\} \right) - \frac{\partial}{\partial \tilde{\beta}} \frac{1}{2\sigma^2} \varepsilon_i^2 \\
&= 0 - \frac{1}{2\sigma^2} \frac{\partial}{\partial \tilde{\beta}} \varepsilon_i^2 \\
&= -\frac{1}{2\sigma^2} 2(\varepsilon_i') \varepsilon_i \\
&= -\frac{1}{\sigma^2} (-\tilde{x}_i \varepsilon_i) \\
&= \frac{1}{\sigma^2} \tilde{x}_i \varepsilon_i
\end{aligned}
$$

$$
\begin{aligned}
\ell_{\tilde{\beta}}' &\stackrel{\text{def}}{=} \frac{\partial}{\partial \tilde{\beta}} \ell_{\tilde{\beta}} \\
&= \frac{\partial}{\partial \tilde{\beta}} \sum_{i=1}^{n} \ell_i \\
&= \sum_{i=1}^{n} \frac{\partial}{\partial \tilde{\beta}} \ell_i \\
&= \sum_{i=1}^{n} \ell_i' \\
&= \sum_{i=1}^{n} \frac{1}{\sigma^2} \tilde{x}_i \varepsilon_i \\
&= \frac{1}{\sigma^2} \sum_{i=1}^{n} \tilde{x}_i \varepsilon_i \\
&= \frac{1}{\sigma^2} \mathbf{X}^\top \tilde{\varepsilon}
\end{aligned}
$$

2.3.4. Hessian

$$
\begin{aligned}
\ell_i'' &\stackrel{\text{def}}{=} \frac{\partial}{\partial \tilde{\beta}^\top} \frac{\partial}{\partial \tilde{\beta}} \ell_i \\
&= \frac{\partial}{\partial \tilde{\beta}^\top} \ell_i' \\
&= \frac{\partial}{\partial \tilde{\beta}^\top} \left(\frac{1}{\sigma^2} \tilde{x}_i \varepsilon_i \right) \\
&= \frac{1}{\sigma^2} \tilde{x}_i \varepsilon_i'^\top \\
&= \frac{1}{\sigma^2} \tilde{x}_i (-\tilde{x}_i^\top) \\
&= -\frac{1}{\sigma^2} \tilde{x}_i \tilde{x}_i^\top
\end{aligned}
$$

$$
\begin{aligned}
\ell'' &\stackrel{\text{def}}{=} \frac{\partial}{\partial \tilde{\beta}^\top} \frac{\partial}{\partial \tilde{\beta}} \ell \\
&= \frac{\partial}{\partial \tilde{\beta}^\top} \ell' \\
&= \frac{\partial}{\partial \tilde{\beta}^\top} \sum_{i=1}^n \ell_i' \\
&= \sum_{i=1}^n \frac{\partial}{\partial \tilde{\beta}^\top} \ell_i' \\
&= \sum_{i=1}^n \ell_i'' \\
&= \sum_{i=1}^n -\frac{1}{\sigma^2} \tilde{x}_i \tilde{x}_i^\top \\
&= -\frac{1}{\sigma^2} \sum_{i=1}^n \tilde{x}_i \tilde{x}_i^\top \\
&= -\frac{1}{\sigma^2} \mathbf{X}^\top \mathbf{X}
\end{aligned}
$$

That is,

$$
\ell'' = -\frac{1}{\sigma^2} \sum_{i=1}^n \tilde{x}_i \tilde{x}_i^\top \tag{2.6}
$$

2.3.5. Alternative approach using matrix derivatives

$$
\begin{aligned}
\ell_{\tilde{\beta}}'(\tilde{y}|\mathbf{x}, \tilde{\beta}, \sigma^2) &\stackrel{\text{def}}{=} \frac{\partial}{\partial \tilde{\beta}} \ell_{\tilde{\beta}}(\tilde{y}|\mathbf{x}, \tilde{\beta}, \sigma^2) \\
&= -\frac{1}{2\sigma^2} \frac{\partial}{\partial \tilde{\beta}} \left(\sum_{i=1}^n \left(y_i - \left(\tilde{x}_i \cdot \tilde{\beta} \right) \right)^2 \right)
\end{aligned} \tag{2.7}
$$

Let's switch to matrix-vector notation:

$$\sum_{i=1}^{n}(y_i - \tilde{x}_i^\top \tilde{\beta})^2 = (\tilde{y} - \mathbf{X}\tilde{\beta}) \cdot (\tilde{y} - \mathbf{X}\tilde{\beta})$$

So

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

We will use some results from vector calculus:

$$\begin{aligned}
\frac{\partial}{\partial\tilde{\beta}}\left(\sum_{i=1}^{n}(y_i - x_i'\beta)^2\right) &= \frac{\partial}{\partial\tilde{\beta}}(\tilde{y} - X\beta)'(\tilde{y} - X\beta) \\
&= \frac{\partial}{\partial\tilde{\beta}}(y'y - 2y'X\beta + \beta'\mathbf{X}'\mathbf{X}\beta) \\
&= (-2X'y + 2\mathbf{X}'\mathbf{X}\beta) \\
&= -2X'(y - X\beta) \\
&= -2X'(y - \mathrm{E}[y]) \\
&= -2X'\varepsilon(y)
\end{aligned} \tag{2.8}$$

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

$$\begin{aligned}
0 &= (-2X'y + 2\mathbf{X}'\mathbf{X}\beta) \\
2X'y &= 2\mathbf{X}'\mathbf{X}\beta \\
X'y &= \mathbf{X}'\mathbf{X}\beta \\
(\mathbf{X}'\mathbf{X})^{-1}X'y &= \beta
\end{aligned}$$

2.3.5.1. Hessian

The Hessian (second derivative matrix) is:

$$\ell''_{\beta,\beta'}(\beta, \sigma^2; \tilde{y}, \mathbf{X}) = -\frac{1}{2\sigma^2}\mathbf{X}'\mathbf{X}$$

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

Similarly (not shown):

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

And

$$\begin{aligned}\mathcal{J}_\beta &= E[-\ell''_{\beta,\beta'}(Y|X, \beta, \sigma^2)] \\ &= \frac{1}{\sigma^2}\mathbf{X}'\mathbf{X}\end{aligned}$$

So:

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

and

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

These are all results you have hopefully seen before.

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

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

Example 2.1 (MLEs for birthweight data)**.** In model 2.2 above, $\hat{\mathcal{J}}(\beta)$ is:

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

Table 2.16.: Covariance matrix of $\hat{\tilde{\beta}}$ for `birthweight` model 2.2 (with interaction term)

```
bw_lm2 |> vcov()
#>             (Intercept)  sexmale        age sexmale:age
#> (Intercept)     1353968 -1353968 -34870.966   34870.966
#> sexmale        -1353968  2596387  34870.966  -67210.974
#> age              -34871    34871    899.896    -899.896
#> sexmale:age       34871   -67211   -899.896    1743.548
```

```
bw_lm2 |>
  vcov() |>
  diag() |>
  sqrt()
#> (Intercept)     sexmale         age sexmale:age
#>   1163.6015   1611.3309     29.9983     41.7558
```

```
bw_lm2 |>
  parameters() |>
  print_md()
```

Table 2.17.: 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	$< .001$
sex (male) $\times$ age	-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.

2.3.6. 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] 180.613
```

2.3.6.1. 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 .
#> sexmale        873.0     1611.3    0.54  0.59395
#> age            130.4       30.0    4.35  0.00031 ***
#> sexmale:age    -18.4       41.8   -0.44  0.66389
#> ---
#> Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 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: see note in `?stats::sigma`

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?

$H_0 : \beta_{AM} = 0$

$H_A : \beta_{AM} \neq 0$

$P(|\hat{\beta}_{AM}| > |-18.417241| \mid H_0) = ?$

2.4.2. Wald tests and CIs

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

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

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

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

2.4.3. P-values

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

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

```
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)
```

$$
\begin{aligned}
&P\Big(|\hat{\beta}_{AM}| > |-18.417241| \Big| H_0\Big) \\
&= \Pr\left(\left|\frac{\hat{\beta}_{AM}}{\hat{SE}(\hat{\beta}_{AM})}\right| > \left|\frac{-18.417241}{41.755817}\right| \Bigg| H_0\right) \\
&= \Pr\left(|T_{20}| > 0.44107 | H_0\right) \\
&= 0.663893
\end{aligned}
$$

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) × age	-18.42	41.76	(-105.52, 68.68)	-0.44	0.664

```
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]   68.6839 -105.5184
```

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) × age	-18.42	41.76	(-105.52, 68.68)	-0.44	0.664

```
pval_z <- pnorm(abs(t_stat), lower = FALSE) * 2

print(pval_z)
#> [1] 0.659162
```

2.4.7. Confidence intervals

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

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

```
confint_radius_z <- se_hat * qnorm(0.975, lower = TRUE)
confint_z <-
  beta_hat + c(-1, 1) * confint_radius_z
print(confint_z)
#> [1] -100.2571   63.4227
```

2.4.8. Likelihood ratio statistics

```
logLik(bw_lm2)
#> 'log Lik.' -156.579 (df=5)
logLik(bw_lm1)
#> 'log Lik.' -156.695 (df=4)

log_LR <- (logLik(bw_lm2) - logLik(bw_lm1)) |> as.numeric()
delta_df <- (bw_lm1$df.residual - df.residual(bw_lm2))


x_max <- 1
```

```r
d_log_LR <- function(x, df = delta_df) dchisq(x, df = df)

chisq_plot <-
  ggplot() +
  geom_function(fun = d_log_LR) +
  stat_function(
    fun = d_log_LR,
    xlim = c(log_LR, x_max),
    geom = "area",
    fill = "gray"
  ) +
  geom_segment(
    aes(
      x = log_LR,
      xend = log_LR,
      y = 0,
      yend = d_log_LR(log_LR)
    ),
    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 2.6.: Chi-square distribution

Now we can get the p-value:

```
pchisq(
  q = 2 * log_LR,
  df = delta_df,
  lower = FALSE
) |>
  print()
#> [1] 0.629806
```

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)
#> # A tibble: 2 x 5
#>   `#Df` LogLik    Df  Chisq `Pr(>Chisq)`
#>   <dbl>  <dbl> <dbl>  <dbl>        <dbl>
#> 1     5  -157.    NA NA           NA
#> 2     4  -157.    -1  0.232        0.630
```

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):

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

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] 323.159

AIC(bw_lm2)
#> [1] 323.159
```

2.5.1.2. BIC in R

```
-2 * logLik(bw_lm2) |> as.numeric() +
  (length(coef(bw_lm2)) + 1) * log(nobs(bw_lm2))
#> [1] 329.049

BIC(bw_lm2)
#> [1] 329.049
```

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 2.23).

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

Example 2.2 (Replicates in the `birthweight` data)**.** In the `birthweight` dataset, there are 2 replicates of the combination "female, age 36" (Table 2.23).

Exercise 2.12 (Replicates in the `birthweight` data)**.** Which covariate pattern(s) in the `birthweight` data has the most replicates?

Table 2.23.: Unique covariate combinations in the `birthweight` data, with replicate counts

```
bw_X_unique
#> # A tibble: 12 x 3
#>    sex      age     n
#>    <fct>  <dbl> <int>
#>  1 female    36     2
#>  2 female    37     1
#>  3 female    38     2
#>  4 female    39     2
#>  5 female    40     4
#>  6 female    42     1
#>  7 male      35     1
#>  8 male      36     1
#>  9 male      37     2
#> 10 male      38     3
#> 11 male      40     4
#> 12 male      41     1
```

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))
#> # A tibble: 2 x 3
#>   sex      age     n
#>   <fct>  <dbl> <int>
#> 1 female    40     4
#> 2 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 2.24.: Saturated model for the `birthweight` data

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

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

```
library(rlang) # defines the `.data` pronoun
plot_PIs_and_CIs <- function(model, data) {
  cis <- model |>
    predict(interval = "confidence") |>
    suppressWarnings() |>
    tibble::as_tibble()
  names(cis) <- paste("ci", names(cis), sep = "_")

  preds <- model |>
    predict(interval = "predict") |>
    suppressWarnings() |>
    tibble::as_tibble()
  names(preds) <- paste("pred", names(preds), sep = "_")
  dplyr::bind_cols(bw, cis, preds) |>
    ggplot2::ggplot() +
    ggplot2::aes(
      x = .data$age,
      y = .data$weight,
      col = .data$sex
    ) +
    ggplot2::geom_point() +
    ggplot2::theme(legend.position = "bottom") +
    ggplot2::geom_line(ggplot2::aes(y = .data$ci_fit)) +
    ggplot2::geom_ribbon(
```

```
      ggplot2::aes(
        ymin = .data$pred_lwr,
        ymax = .data$pred_upr
      ),
      alpha = 0.2
    ) +
    ggplot2::geom_ribbon(
      ggplot2::aes(
        ymin = .data$ci_lwr,
        ymax = .data$ci_upr
      ),
      alpha = 0.5
    ) +
    ggplot2::facet_wrap(~sex)
}
```

```
plot_PIs_and_CIs(bw_lm2, bw)
```

```
plot_PIs_and_CIs(lm_max, bw)
```

(a) Model 2.2 (linear with age:sex interaction)

(b) Saturated model

Figure 2.7.: Model 2.2 and saturated model for `birthweight` data, with confidence and prediction intervals

---

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

```
logLik(lm_max)
#> 'log Lik.' -151.402 (df=13)
```

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

```
lrtest(lm_max, bw_lm2)
#> # A tibble: 2 x 5
#>   `#Df` LogLik    Df Chisq `Pr(>Chisq)`
#>   <dbl>  <dbl> <dbl> <dbl>        <dbl>
#> 1    13  -151.    NA  NA         NA
#> 2     5  -157.    -8  10.4        0.241
```

The likelihood ratio statistic for this test is

$$\lambda = 2 * (\ell_{\text{full}} - \ell) = 10.355374$$

where:

- ℓ_{full} is the log-likelihood of the full model: -151.401601
- ℓ is the log-likelihood of our comparison model (two slopes, two intercepts): -156.579288

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:

```
lm0 <- lm(weight ~ 1, data = bw)

lm0 |>
  parameters() |>
  print_md()
```

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

```
lm0 |> plot_PIs_and_CIs()
```

Figure 2.8.: Null model for birthweight data, with 95% confidence and prediction intervals.

This model also has a likelihood:

```
logLik(lm0)
#> 'log Lik.' -168.955 (df=2)
```

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

```
lrtest(bw_lm2, lm0)
#> # A tibble: 2 x 5
#>   `#Df` LogLik    Df Chisq `Pr(>Chisq)`
#>   <dbl>  <dbl> <dbl> <dbl>        <dbl>
#> 1     5  -157.    NA  NA     NA
#> 2     2  -169.    -3  24.8    0.0000174
```

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

$$\lambda = 2 * (\ell_{\text{full}} - \ell_0) = 35.106732$$

where:

- ℓ_0 is the log-likelihood of the null model: -168.954967
- ℓ_{full} is the log-likelihood of the maximal model: -151.401601

In R, this test is:

```
lrtest(lm_max, lm0)
#> # A tibble: 2 x 5
#>   `#Df` LogLik    Df Chisq `Pr(>Chisq)`
#>   <dbl>  <dbl> <dbl> <dbl>        <dbl>
#> 1    13  -151.    NA  NA      NA
#> 2     2  -169.   -11  35.1     0.000238
```

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
  )

lm1_c <- lm(weight ~ sex + `age - 36wks`, data = bw)

lm2_c <- lm(weight ~ sex + `age - 36wks` + sex:`age - 36wks`, data = bw)

parameters(lm2_c, 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 - 36wks	130.40	30.00	(67.82, 192.98)	4.35	< .001
sex (male) × age - 36wks	-18.42	41.76	(-105.52, 68.68)	-0.44	0.664

Compare with what we got without rescaling:

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

Parameter	Coefficient	SE	95% CI	t(20)	p
(Intercept)	-2141.67	1163.60	(-4568.90, 285.56)	-1.84	0.081
sex (male)	872.99	1611.33	(-2488.18, 4234.17)	0.54	0.594
age	130.40	30.00	(67.82, 192.98)	4.35	< .001
sex (male) × age	-18.42	41.76	(-105.52, 68.68)	-0.44	0.664

2.7. Prediction

2.7.1. Prediction for linear models

Definition 2.2 (Predicted value)**.** In a regression model $\mathrm{p}(y|\tilde{x})$, the **predicted value** of y given $\tilde{x}$ is the estimated mean of Y given $\tilde{X} = \tilde{x}$:

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

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:

$$\begin{aligned}\hat{y} &= \hat{\mathrm{E}}\left[Y|\tilde{X} = \tilde{x}\right] \\ &= \tilde{x}'\hat{\beta} \\ &= \hat{\beta}_0 \cdot 1 + \hat{\beta}_1 x_1 + \ldots + \hat{\beta}_p x_p\end{aligned}$$

2.7.2. Example: prediction for the `birthweight` data

```
x <- c(1, 1, 40)
sum(x * coef(bw_lm1))
#> [1] 3225.49
```

R has built-in functions for prediction:

```
x <- tibble(age = 40, sex = "male")
bw_lm1 |> predict(newdata = x)
#>       1
#> 3225.49
```

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

```
predict(bw_lm1)
#>       1       2       3       4       5       6       7       8       9      10
#> 3225.49 3062.45 2983.70 2578.87 3225.49 3062.45 2621.02 2820.66 2741.91 3304.24
#>      11      12      13      14      15      16      17      18      19      20
#> 2862.81 2941.56 3346.38 3062.45 3225.49 2699.77 2862.81 2578.87 2983.70 2820.66
#>      21      22      23      24
#> 3225.49 2941.56 2983.70 3062.45
```

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

Definition 2.3. For a given dataset $(\tilde{Y}, \mathbf{X})$ and corresponding fitted model $\mathrm{p}_{\hat{\beta}}(\tilde{y}|\mathbf{x})$, the **fitted value** of y_i is the predicted value of y when $\tilde{X} = \tilde{x}_i$ using the estimate parameters $\hat{\beta}$.

R has an extra function to get these values:

```
fitted(bw_lm1)
#>       1       2       3       4       5       6       7       8       9      10
#> 3225.49 3062.45 2983.70 2578.87 3225.49 3062.45 2621.02 2820.66 2741.91 3304.24
#>      11      12      13      14      15      16      17      18      19      20
#> 2862.81 2941.56 3346.38 3062.45 3225.49 2699.77 2862.81 2578.87 2983.70 2820.66
#>      21      22      23      24
#> 3225.49 2941.56 2983.70 3062.45
```

2.7.3. Confidence intervals

Use `predict(se.fit = TRUE)` to compute SEs for predicted values:

```
bw_lm1 |>
  predict(
    newdata = x,
    se.fit = TRUE
  )
#> $fit
#>       1
#> 3225.49
#>
#> $se.fit
#> [1] 61.4599
#>
#> $df
#> [1] 21
#>
#> $residual.scale
#> [1] 177.116
```

The output of `predict.lm(se.fit = TRUE)` is a `list()`; you can extract the elements with `$` or `magrittr::use_series()`:

```
library(magrittr)
bw_lm1 |>
  predict(
    newdata = x,
    se.fit = TRUE
  ) |>
  use_series(se.fit)
#> [1] 61.4599
```

We can construct **confidence intervals** for $\mathrm{E}[Y|X = x]$ using the usual formula:

$$\mu(\tilde{x}) \in (\hat{\mu}(\tilde{x}) \pm \zeta_\alpha)$$

$$\zeta_\alpha = t_{n-p}\left(1 - \frac{\alpha}{2}\right) * \widehat{\mathrm{se}}(\hat{\mu}(\tilde{x}))$$

$$\hat{\mu}(\tilde{x}) = \tilde{x} \cdot \hat{\beta}$$

$$\begin{aligned}
\mathrm{se}(\hat{\mu}(\tilde{x})) &= \sqrt{\mathrm{Var}(\hat{\mu}(\tilde{x}))} \\
\mathrm{Var}(\hat{\mu}(\tilde{x})) &= \mathrm{Var}\left(x'\hat{\beta}\right) \\
&= x'\mathrm{Var}\left(\hat{\beta}\right)x \\
&= x'\sigma^2(\mathbf{X}'\mathbf{X})^{-1}x \\
&= \sigma^2 x'(\mathbf{X}'\mathbf{X})^{-1}x \\
&= \sum_{i=1}^{n}\sum_{j=1}^{n} x_i x_j \mathrm{Cov}\left(\hat{\beta}_i, \hat{\beta}_j\right) \\
\widehat{\mathrm{Var}}(\hat{\mu}(\tilde{x})) &= \hat{\sigma}^2 x'(\mathbf{X}'\mathbf{X})^{-1}x
\end{aligned}$$

```r
bw_lm2 |> predict(
  newdata = x,
  interval = "confidence"
)
#>       fit     lwr     upr
#> 1 3210.64 3062.23 3359.05
```

```r
library(sjPlot)
bw_lm2 |>
  plot_model(type = "pred", terms = c("age", "sex"), show.data = TRUE) +
  theme_sjplot() +
  theme(legend.position = "bottom")
```

Figure 2.9.: Predicted values and confidence bands for the `birthweight` model with interaction term

2.7.4. Prediction intervals

We can also construct **prediction intervals** for the value of a new observation Y^*, given a covariate pattern $\tilde{x}^*$:

$$
\begin{aligned}
\hat{Y}^* &= \hat{\mu}(\tilde{x}^*) + \hat{\epsilon}^* \\
\mathrm{Var}\left(\hat{Y}\right) &= \mathrm{Var}(\hat{\mu}) + \mathrm{Var}(\hat{\epsilon}) \\
\mathrm{Var}\left(\hat{Y}\right) &= \mathrm{Var}\left(x'\hat{\beta}\right) + \mathrm{Var}(\hat{\epsilon}) \\
&= \tilde{x}^{*\top}\mathrm{Var}\left(\hat{\beta}\right)\tilde{x}^* + \sigma^2 \\
&= \tilde{x}^{*\top}(\sigma^2(\mathbf{X}'\mathbf{X})^{-1})\tilde{x}^* + \sigma^2 \\
&= \sigma^2\tilde{x}^{*\top}(\mathbf{X}'\mathbf{X})^{-1}\tilde{x}^* + \sigma^2
\end{aligned}
\tag{2.9}
$$

See Hogg, Tanis, and Zimmerman (2015) §7.6 (p. 340) for a longer version.

```r
bw_lm2 |>
  predict(newdata = x, interval = "predict")
#>       fit     lwr     upr
#> 1 3210.64 2805.71 3615.57
```

If you don't specify `newdata`, you get a warning:

```
bw_lm2 |>
  predict(interval = "predict") |>
  head()
#> Warning in predict.lm(bw_lm2, interval = "predict"): predictions on current data refer t
#>       fit     lwr     upr
#> 1 2552.73 2124.50 2980.97
#> 2 2552.73 2124.50 2980.97
#> 3 2683.13 2275.99 3090.27
#> 4 2813.53 2418.60 3208.47
#> 5 2813.53 2418.60 3208.47
#> 6 2943.93 2551.48 3336.38
```

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.

```
plot_PIs_and_CIs(bw_lm2, bw)
```

Figure 2.10.: Confidence and prediction intervals for `birthweight` model 2.2

2.8. Diagnostics

> **Tip**
>
> This section is adapted from Dobson and Barnett (2018, secs. 6.2–6.3) and Dunn and Smyth (2018) Chapter 3[a].
>
> [a] https://link.springer.com/chapter/10.1007/978-1-4419-0118-7_3

2.8.1. Assumptions in linear regression models

$$Y_i|\tilde{X}_i \sim_{\perp\!\!\!\perp} \mathrm{N}(\mu_i, \sigma^2)$$
$$\mu_i = \tilde{x} \cdot \tilde{\beta}$$

1. Normality

The model assumes that the distribution conditional on a given X value is Gaussian.

2. Correct Functional Form of Conditional Mean Structure (Linear Component)

The model assumes that the conditional means have the structure:

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

3. Homoskedasticity

The model assumes that variance σ^2 is constant (with respect to $\tilde{x}$).

4. Independence

The model assumes that 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 2.11.: 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.

2.8.2.1. Fitted model for `hers` data

Consider the `hers` data from Vittinghoff et al. (2012).

The "heart and estrogen/progestin study" (HERS) was 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).

Suppose we consider models with and without intercept terms (i.e., possibly forcing the intercept to go through 0):

```
hers_lm_with_int <- lm(
  na.action = na.exclude,
  LDL ~ smoking * age, data = hers
)


library(equatiomatic)
equatiomatic::extract_eq(hers_lm_with_int)
```

Table 2.28.: `hers` data

```
hers <- fs::path_package("rme", "extdata/hersdata.dta") |>
  haven::read_dta()
hers
#> # A tibble: 2,763 x 37
#>    HT             age raceth  nonwhite smoking drinkany exercise physact globrat
#>    <dbl+lbl>    <dbl> <dbl+l> <dbl+lb> <dbl+l> <dbl+lb> <dbl+lb> <dbl+l> <dbl+l>
#>  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]  0 [no]   0 [no]   1 [muc~ 3 [goo~
#>  3 1 [hormone ~    69 1 [Whi~ 0 [no]   0 [no]  0 [no]   0 [no]   3 [abo~ 3 [goo~
#>  4 0 [placebo]     64 1 [Whi~ 0 [no]   1 [yes] 1 [yes]  0 [no]   1 [muc~ 3 [goo~
#>  5 0 [placebo]     65 1 [Whi~ 0 [no]   0 [no]  0 [no]   0 [no]   2 [som~ 3 [goo~
#>  6 1 [hormone ~    68 2 [Afr~ 1 [yes]  0 [no]  1 [yes]  0 [no]   3 [abo~ 3 [goo~
#>  7 0 [placebo]     70 1 [Whi~ 0 [no]   0 [no]  0 [no]   0 [no]   3 [abo~ 2 [fai~
#>  8 1 [hormone ~    69 1 [Whi~ 0 [no]   0 [no]  0 [no]   1 [yes]  5 [muc~ 4 [ver~
#>  9 1 [hormone ~    61 1 [Whi~ 0 [no]   0 [no]  1 [yes]  1 [yes]  3 [abo~ 4 [ver~
#> 10 1 [hormone ~    62 1 [Whi~ 0 [no]   1 [yes] 1 [yes]  0 [no]   2 [som~ 3 [goo~
#> # i 2,753 more rows
#> # 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>
```

Table 2.29.: `hers` data models with and without intercepts

(a) With intercept

```
library(gtsummary)
hers_lm_with_int |>
  tbl_regression(intercept = TRUE)
```

Characteristic	Beta	95% CI	p-value
(Intercept)	154	138, 170	<0.001
current smoker	54	15, 94	0.007
age in years	-0.14	-0.38, 0.09	0.2
current smoker * age in years	-0.79	-1.4, -0.17	0.012

Abbreviation: CI = Confidence Interval

(b) No intercept

```
hers_lm_no_int |>
  tbl_regression(intercept = TRUE)
```

Characteristic	Beta	95% CI	p-value
age in years	2.1	2.1, 2.2	<0.001
age in years * current smoker	0.19	0.12, 0.26	<0.001

Abbreviation: CI = Confidence Interval

$$\text{LDL} = \alpha + \beta_1(\text{smoking}) + \beta_2(\text{age}) + \beta_3(\text{smoking} \times \text{age}) + \epsilon \tag{2.10}$$

```
hers_lm_no_int <- lm(
  na.action = na.exclude,
  LDL ~ age + smoking:age - 1, data = hers
)

library(equatiomatic)
equatiomatic::extract_eq(hers_lm_no_int)
```

$$\text{LDL} = \beta_1(\text{age}) + \beta_2(\text{age} \times \text{age}_{\text{smoking}}) + \epsilon \tag{2.11}$$

```r
library(sjPlot)

hers_plot1 <- hers_lm_no_int |>
  sjPlot::plot_model(
    type = "pred",
    terms = c("age", "smoking"),
    show.data = TRUE
  ) +
  facet_wrap(~group_col, ncol = 1) +
  expand_limits(y = 0) +
  theme(legend.position = "bottom")

hers_plot1
```

```r
library(sjPlot)

hers_plot2 <- hers_lm_with_int |>
  sjPlot::plot_model(
    type = "pred",
    terms = c("age", "smoking"),
    show.data = TRUE
  ) +
  facet_wrap(~group_col, ncol = 1) +
  expand_limits(y = 0) +
  theme(legend.position = "bottom")

hers_plot2
```

(a) No intercept

(b) With intercept

Figure 2.12.: `hers` data models with and without intercepts

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/deviation from the population mean)**.** The **residual noise** in a probabilistic model $p(Y)$, also known as the **residual deviation of an observation from its population mean** or **residual** for short, is the difference between an observed value y and its population mean:

$$\varepsilon(y) \stackrel{\text{def}}{=} y - \mathrm{E}[Y] \tag{2.12}$$

We use the same notation for residual noise that we used for errors.

$\mathrm{E}[Y]$ can be viewed as an estimate of Y, before y is observed. Conversely, each observation y can be viewed as an estimate of $\mathrm{E}[Y]$ (albeit an imprecise one, individually, since $n = 1$).

We can rearrange Equation 2.12 to view y as the sum of its mean plus the residual noise:

$$y = \mathrm{E}[Y] + \varepsilon(y)$$

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

Proof. Left to the reader. □

Definition 2.5 (Residuals of a fitted model value)**.** The **residual of a fitted value** $\hat{y}$ (shorthand: "residual") is its error relative to the observed data:

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

Example 2.3 (residuals in `birthweight` data)**.**

```
plot1_interact +
  facet_wrap(~sex) +
  geom_segment(
    aes(
      x = age,
      y = predlm2,
      xend = age,
      yend = weight,
      col = sex,
      group = id
    ),
    linetype = "dotted"
  )
```

Figure 2.13.: Fitted values and residuals for interaction model for `birthweight` data

---

2.8.3.1. Residuals of fitted values vs residual noise

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

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

2.8.3.2. General characteristics of residuals

Theorem 2.2. *If $\hat{E}[Y]$ is an unbiased estimator of the mean $E[Y]$, then:*

$$E[e(y)] = 0 \tag{2.13}$$

$$Var(e(y)) \approx \sigma^2 \tag{2.14}$$

Proof.

Equation 2.13:

$$\begin{aligned} \mathrm{E}[e(y)] &= \mathrm{E}[y - \hat{y}] \\ &= \mathrm{E}[y] - \mathrm{E}[\hat{y}] \\ &= \mathrm{E}[y] - \mathrm{E}[y] \\ &= 0 \end{aligned}$$

Equation 2.14:

$$\begin{aligned} \mathrm{Var}(e(y)) &= \mathrm{Var}(y - \hat{y}) \\ &= \mathrm{Var}(y) + \mathrm{Var}(\hat{y}) - 2\mathrm{Cov}(y, \hat{y}) \\ &\dot{\approx} \mathrm{Var}(y) + 0 - 2 \cdot 0 \\ &= \mathrm{Var}(y) \\ &= \sigma^2 \end{aligned}$$

□

2.8.3.3. 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 $\hat{\sigma}^2$; that is:

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

2.8.3.4. Computing residuals in R

R provides a function for residuals:

```
resid(bw_lm2)
#>         1         2         3         4         5         6         7         8
#>  176.2667 -140.7333 -144.1333  -59.5333  177.4667 -126.9333  -68.9333  242.6667
#>         9        10        11        12        13        14        15        16
#> -139.3333   51.6667  156.6667 -125.1333  274.2759 -137.7069  -27.6897 -246.6897
#>        17        18        19        20        21        22        23        24
#> -191.6724  189.3276  -11.6724 -242.6379  -47.6379  262.3621  210.3621  -30.6207
```

Exercise 2.13. Check R's output by computing the residuals directly.

Solution.

```
bw$weight - fitted(bw_lm2)
#>         1         2         3         4         5         6         7         8
#>  176.2667 -140.7333 -144.1333  -59.5333  177.4667 -126.9333  -68.9333  242.6667
#>         9        10        11        12        13        14        15        16
#> -139.3333   51.6667  156.6667 -125.1333  274.2759 -137.7069  -27.6897 -246.6897
#>        17        18        19        20        21        22        23        24
#> -191.6724  189.3276  -11.6724 -242.6379  -47.6379  262.3621  210.3621  -30.6207
```

This matches R's output!

2.8.3.5. Graphing the residuals

```
plot1_interact +
  facet_wrap(~sex) +
  geom_segment(
    aes(
      x = age,
      y = predlm2,
      xend = age,
      yend = weight,
      col = sex,
      group = id
    ),
    linetype = "dotted"
  )
```

(a) fitted values

```
bw <- bw |>
  mutate(
    resids_intxn =
      weight - fitted(bw_lm2)
  )

plot_bw_resid <-
  bw |>
  ggplot(aes(
    x = age,
    y = resids_intxn,
    linetype = sex,
    shape = sex,
    col = sex
  )) +
  theme_bw() +
  xlab("Gestational age (weeks)") +
  ylab("residuals (grams)") +
  theme(legend.position = "bottom") +
  geom_hline(aes(
    yintercept = 0,
    col = sex
  )) +
  geom_segment(
    aes(yend = 0),
    linetype = "dotted"
  ) +
  geom_point()
# expand_limits(y = 0, x = 0) +
geom_point(alpha = .7)
#> geom_point: na.rm = FALSE
#> stat_identity: na.rm = FALSE
#> position_identity
print(plot_bw_resid + facet_wrap(~sex))
```

(b) Residuals

Figure 2.14.: Fitted values and residuals for interaction model for `birthweight` data

2.8.3.6. Residuals versus predictors

```
hers <- hers |>
  mutate(
    resids_no_intcpt =
      LDL - fitted(hers_lm_no_int),
    resids_with_intcpt =
      LDL - fitted(hers_lm_with_int)
  )
```

```
hers |>
  arrange(age) |>
  ggplot() +
  aes(x = age, y = resids_no_intcpt,
  geom_point() +
  geom_hline(aes(yintercept = 0, col
  facet_wrap(~smoking, labeller = "la
  theme(legend.position = "bottom") +
  geom_smooth(col = "blue")
```

```
hers |>
  arrange(age) |>
  ggplot() +
  aes(x = age, y = resids_with_intcpt, col = factor(sm
  geom_point() +
  geom_hline(aes(yintercept = 0, col = factor(smoking)
  facet_wrap(~smoking, labeller = "label_both") +
  theme(legend.position = "bottom") +
  geom_smooth(col = "blue")
```

(a) no intercept

(b) with intercept

Figure 2.15.: Residuals of `hers` data vs predictors

2.8.3.7. Residuals versus fitted values

If the model contains multiple continuous covariates, how do we check for errors in the mean structure assumption?

```
library(ggfortify)
hers_lm_no_int |>
  update(na.action = na.omit) |>
  autoplot(
```

```
    which = 1,
    ncol = 1,
    smooth.colour = NA
  ) +
  geom_hline(yintercept = 0, col = "red")
```

Figure 2.16.: Residuals of interaction model for `hers` data

We can add a LOESS smooth to visualize where the residual mean is nonzero:

```
library(ggfortify)
hers_lm_no_int |>
  update(na.action = na.omit) |>
  autoplot(
    which = 1,
    ncol = 1
  ) +
  geom_hline(yintercept = 0, col = "red")
```

Figure 2.17.: Residuals of interaction model for `hers` data, no intercept term

---

```
library(ggfortify)
hers_lm_no_int |>
  update(na.action = na.omit) |>
  autoplot(
    which = 1,
    ncol = 1
  ) +
  geom_hline(yintercept = 0, col = "red")
```

```
hers_lm_with_int |>
  update(na.action = na.omit) |>
  autoplot(
    which = 1,
    ncol = 1
  ) +
  geom_hline(yintercept = 0, col = "red")
```

(a) no intercept term

(b) with intercept term

Figure 2.18.: Residuals of interaction model for `hers` data, with and without intercept term

---

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,

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

2.8.4. Marginal distributions of residuals

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

2.8.4.1. Standardized residuals in R

```
rstandard(bw_lm2)
#>          1          2          3          4          5          6          7
#>  1.1598166 -0.9260109 -0.8747917 -0.3472255  1.0350665 -0.7347315 -0.3990086
#>          8          9         10         11         12         13         14
#>  1.4375164 -0.8253872  0.3060646  0.9280669 -0.8761592  1.9142780 -0.8655921
#>         15         16         17         18         19         20         21
#> -0.1642993 -1.4637574 -1.1101599  1.0965787 -0.0676062 -1.4615865 -0.2869582
#>         22         23         24
#>  1.5803994  1.2671652 -0.1980543
resid(bw_lm2) / sigma(bw_lm2)
#>          1          2          3          4          5          6          7
#>  0.9759331 -0.7791962 -0.7980209 -0.3296173  0.9825771 -0.7027900 -0.3816622
#>          8          9         10         11         12         13         14
#>  1.3435690 -0.7714449  0.2860621  0.8674141 -0.6928239  1.5185792 -0.7624398
#>         15         16         17         18         19         20         21
#> -0.1533089 -1.3658431 -1.0612299  1.0482473 -0.0646265 -1.3434099 -0.2637562
#>         22         23         24
#>  1.4526163  1.1647086 -0.1695371
```

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_alt = weight - fitted_lm2,
    std_resid_lm2 = rstandard(bw_lm2),
    std_resid_lm2_alt = resid_lm2 / sigma(bw_lm2)
  )

bw |>
  select(
    sex,
    age,
    weight,
    fitted_lm2,
    resid_lm2,
    std_resid_lm2
  )
#> # A tibble: 24 x 6
#>    sex      age weight fitted_lm2 resid_lm2 std_resid_lm2
#>    <fct>  <dbl>  <dbl>      <dbl>     <dbl>         <dbl>
#>  1 female    36   2729      2553.     176.          1.16
#>  2 female    36   2412      2553.    -141.         -0.926
#>  3 female    37   2539      2683.    -144.         -0.875
#>  4 female    38   2754      2814.     -59.5        -0.347
#>  5 female    38   2991      2814.     177.          1.04
#>  6 female    39   2817      2944.    -127.         -0.735
#>  7 female    39   2875      2944.     -68.9        -0.399
#>  8 female    40   3317      3074.     243.          1.44
#>  9 female    40   2935      3074.    -139.         -0.825
#> 10 female    40   3126      3074.      51.7         0.306
#> # i 14 more rows
```

Now let's build histograms:

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

print(resid_marginal_hist)
```

Figure 2.19.: 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 2.20.: 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 and Smyth (2018) §3.5.4[6].

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
    )
  ) +
```

[6] 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

```
  geom_point() +
  theme_classic() +
  theme(legend.position = "none") + # removing the plot legend
  ggtitle("Normal Q-Q") +
  xlab("Theoretical Quantiles") +
  ylab("Standardized residuals")

# find the expected line:

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)
```

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 the linear component of the mean,

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

Then 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 2.21).

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

Figure 2.21.: `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,

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

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 2.22.: 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)
```

(a) Data and fit

(b) Residuals vs fitted

Figure 2.23.: Number of authors versus title length in *PLOS Medicine*, with linear model fit

---

Quadratic fit

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

```
fig3 =
  fig2 +
geom_smooth(
    method = "lm",
    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)
```

(a) Data and fit

(b) Residuals vs fitted

Figure 2.24.: 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)
```

(a) Linear

(b) Quadratic

Figure 2.25.: 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)
```

(a) Data and fit

(b) Residuals vs fitted

Figure 2.26.: 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)
```

Table 2.30.: linear vs quadratic

```
anova(lm_PLOS_linear, lm_PLOS_quad)
#> # A tibble: 2 x 6
#>   Res.Df     RSS    Df `Sum of Sq`     F  `Pr(>F)`
#>    <dbl>   <dbl> <dbl>       <dbl> <dbl>     <dbl>
#> 1    876 947502.    NA         NA   NA   NA
#> 2    875 880950.     1      66552.  66.1  1.46e-15
```

Table 2.31.: quadratic vs cubic

```
anova(lm_PLOS_quad, lm_PLOS_cub)
#> # A tibble: 2 x 6
#>   Res.Df     RSS    Df `Sum of Sq`     F  `Pr(>F)`
#>    <dbl>   <dbl> <dbl>       <dbl> <dbl>     <dbl>
#> 1    875 880950.    NA         NA   NA   NA
#> 2    874 865933.     1      15018.  15.2  0.000106
```

(a) Data and fit

(b) Residuals vs fitted

Figure 2.27.: logarithmic fit

Model selection

AIC/BIC

```
AIC(lm_PLOS_quad)
#> [1] 8567.61
AIC(lm_PLOS_cub)
#> [1] 8554.51
```

```
AIC(lm_PLOS_cub)
#> [1] 8554.51
AIC(lm_PLOS_log)
#> [1] 8543.63
```

```
BIC(lm_PLOS_cub)
#> [1] 8578.4
BIC(lm_PLOS_log)
#> [1] 8557.97
```

Extrapolation is dangerous

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

Figure 2.28.: 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 2.29).

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

Figure 2.29.: 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.

```
autoplot(bw_lm2, which = 5, ncol = 1) |> print()
```

Figure 2.30.: `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**, $\mathrm{E}[(y - \hat{y})^2]$, for new observations that weren't in our data set when we fit the model.

Unfortunately,

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

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

2.9.1.1. Cross-validation

```
data("carbohydrate", package = "dobson")
library(cvTools)
full_model <- lm(carbohydrate ~ ., data = carbohydrate)
cv_full <-
  full_model |> cvFit(
    data = carbohydrate, K = 5, R = 10,
    y = carbohydrate$carbohydrate
  )

reduced_model <- full_model |> update(formula = ~ . - age)

cv_reduced <-
  reduced_model |> cvFit(
    data = carbohydrate, K = 5, R = 10,
    y = carbohydrate$carbohydrate
  )
```

```
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)$adj.r.squared,
  sigma(full_model),
  logLik(full_model) |> as.numeric(),
  "reduced",
  cv_reduced$cv,
  summary(reduced_model)$r.squared,
  summary(reduced_model)$adj.r.squared,
  sigma(reduced_model),
  logLik(reduced_model) |> as.numeric()
)

compare_results
#> # A tibble: 2 x 6
#>   model   cvRMSE r.squared adj.r.squared trainRMSE loglik
#>   <chr>    <dbl>     <dbl>         <dbl>     <dbl>  <dbl>
#> 1 full      6.88     0.481         0.383      5.96  -61.8
#> 2 reduced   7.03     0.445         0.380      5.97  -62.5
```

```
anova(full_model, reduced_model)
#> # A tibble: 2 x 6
#>   Res.Df   RSS    Df `Sum of Sq`     F `Pr(>F)`
#>    <dbl> <dbl> <dbl>       <dbl> <dbl>    <dbl>
#> 1     16  568.    NA        NA   NA      NA
#> 2     17  606.    -1       -38.4  1.08    0.314
```

2.9.1.2. stepwise regression

```
library(olsrr)
olsrr:::ols_step_both_aic(full_model)
#>
#>
#>                                Stepwise Summary
#> --------------------------------------------------------------------------
#> Step    Variable         AIC        SBC       SBIC       R2       Adj. R2
#> --------------------------------------------------------------------------
#>  0      Base Model     140.773    142.764    83.068    0.00000    0.00000
#>  1      protein (+)    137.950    140.937    80.438    0.21427    0.17061
#>  2      weight (+)     132.981    136.964    77.191    0.44544    0.38020
#> --------------------------------------------------------------------------
#>
#> Final Model Output
#> ------------------
#>
#>                           Model Summary
#> ---------------------------------------------------------------
#> R                       0.667       RMSE                 5.505
#> R-Squared               0.445       MSE                 30.301
#> Adj. R-Squared          0.380       Coef. Var           15.879
#> Pred R-Squared          0.236       AIC                132.981
#> MAE                     4.593       SBC                136.964
#> ---------------------------------------------------------------
#>  RMSE: Root Mean Square Error
#>  MSE: Mean Square Error
#>  MAE: Mean Absolute Error
#>  AIC: Akaike Information Criteria
#>  SBC: Schwarz Bayesian Criteria
#>
#>                                ANOVA
#> -------------------------------------------------------------------
#>                 Sum of
#>                Squares        DF    Mean Square      F        Sig.
#> -------------------------------------------------------------------
#> Regression     486.778         2        243.389    6.827    0.0067
#> Residual       606.022        17         35.648
```

```
#> Total         1092.800        19
#> ----------------------------------------------------------------
#>
#>                                   Parameter Estimates
#> ---------------------------------------------------------------------------------------
#>       model      Beta    Std. Error    Std. Beta      t        Sig      lower     upper
#> ---------------------------------------------------------------------------------------
#> (Intercept)    33.130        12.572                  2.635    0.017     6.607    59.654
#>     protein     1.824         0.623        0.534     2.927    0.009     0.509     3.139
#>      weight    -0.222         0.083       -0.486    -2.662    0.016    -0.397    -0.046
#> ---------------------------------------------------------------------------------------
```

2.9.1.3. Lasso

$$\arg\max_{\theta} \left\{ \ell(\theta) - \lambda \sum_{j=1}^{p} |\beta_j| \right\}$$

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

```r
autoplot(fit, xvar = "lambda")
```

Figure 2.31.: Lasso selection

```
cvfit <- cv.glmnet(x, y)
plot(cvfit)
```

Table 2.32.: The `iris` data

```
head(iris)
#> # A tibble: 6 x 5
#>   Sepal.Length Sepal.Width Petal.Length Petal.Width Species
#>          <dbl>       <dbl>        <dbl>       <dbl> <fct>
#> 1          5.1         3.5          1.4         0.2 setosa
#> 2          4.9         3            1.4         0.2 setosa
#> 3          4.7         3.2          1.3         0.2 setosa
#> 4          4.6         3.1          1.5         0.2 setosa
#> 5          5           3.6          1.4         0.2 setosa
#> 6          5.4         3.9          1.7         0.4 setosa
```

```
coef(cvfit, s = "lambda.1se")
#> 4 x 1 sparse Matrix of class "dgCMatrix"
#>             lambda.1se
#> (Intercept)  34.109015
#> age           .
#> weight       -0.104061
#> protein       0.944061
```

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 2.32 shows the (in)famous[7] `iris` data (Anderson (1935)), and Table 2.33 provides summary statistics. The data include three species: "setosa", "versicolor", and "virginica".

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

[7] https://www.meganstodel.com/posts/no-to-iris/

Table 2.33.: Summary statistics for the `iris` data

	setosa (N=50)	versicolor (N=50)	virginica (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]

```
  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 $X = 3$.

Then we could fit a model like:

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

Table 2.35.: 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	0.46	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,
```

Table 2.34.: `iris` data with numeric coding of species

```
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
    )
  )

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

```
      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 2.32.: 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 2.36.: 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 (versicolor)	0.93	0.10	(0.73, 1.13)	9.03	< .001
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_lm2_no_int <- lm(Sepal.Length ~ Species - 1, data = iris)
iris_lm2_no_int |>
  parameters() |>
  print_md()
```

Table 2.37.

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

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

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

print(iris_plot2)
```

Figure 2.33.

Table 2.38.

```
formula(iris_lm2)
#> Sepal.Length ~ Species
model.matrix(iris_lm2) |>
  as_tibble() |>
  unique()
#> # A tibble: 3 x 3
#>   `(Intercept)` Speciesversicolor Speciesvirginica
#>           <dbl>             <dbl>            <dbl>
#> 1             1                 0                0
#> 2             1                 1                0
#> 3             1                 0                1
```

Table 2.39.

```
formula(iris_lm2_no_int)
#> Sepal.Length ~ Species - 1
model.matrix(iris_lm2_no_int) |>
  as_tibble() |>
  unique()
#> # A tibble: 3 x 3
#>   Speciessetosa Speciesversicolor Speciesvirginica
#>           <dbl>             <dbl>            <dbl>
#> 1             1                 0                0
#> 2             0                 1                0
#> 3             0                 0                1
```

2.10.7. Let's see how R did that:

This format is called a "corner point parametrization" (e.g., in Dobson and Barnett (2018)) or "treatment coding" (e.g., in Dunn and Smyth (2018)).

The default contrasts are controlled by `options("contrasts")`:

```
options("contrasts")
#> $contrasts
#>         unordered           ordered
#> "contr.treatment"      "contr.poly"
```

See `?options` for more details.

This format is called a "group point parametrization" (e.g., in Dobson and Barnett (2018)).

Table 2.40.: HERS dataset

```
hers |> head()
#> # A tibble: 6 x 37
#>   HT              age raceth  nonwhite smoking drinkany exercise physact globrat
#>   <dbl+lbl>     <dbl> <dbl+l> <dbl+lb> <dbl+l> <dbl+lb> <dbl+lb> <dbl+l> <dbl+l>
#> 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]  0 [no]   0 [no]   1 [muc~ 3 [goo~
#> 3 1 [hormone t~    69 1 [Whi~ 0 [no]   0 [no]  0 [no]   0 [no]   3 [abo~ 3 [goo~
#> 4 0 [placebo]      64 1 [Whi~ 0 [no]   1 [yes] 1 [yes]  0 [no]   1 [muc~ 3 [goo~
#> 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>
```

There are more options; see Dobson and Barnett (2018) §6.4.1 and the `codingMatrices` package[8] vignette[9] (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()` function[10].

Example 2.4.

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

Check out `?codingMatrices::contr.diff`

[8] https://CRAN.R-project.org/package=codingMatrices
[9] https://cran.r-project.org/web/packages/codingMatrices/vignettes/codingMatrices.pdf
[10] or equivalently, `factor(ordered = TRUE)`

3. Models for Binary Outcomes

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(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' = 6)

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 default
legend_text_size = 9
run_graphs = TRUE
```

```
options(digits = 6)
```

Acknowledgements

This content is adapted from:

- Dobson and Barnett (2018), Chapter 7
- Vittinghoff et al. (2012), Chapter 5
- David Rocke[1]'s materials from the 2021 edition of Epi 204[2]
- Nahhas (2024) Chapter 6[3]

3.1. Introduction

Exercise 3.1. What is logistic regression?

Solution 3.1.

Definition 3.1. **Logistic regression** is a framework for modeling binary outcomes, conditional on one or more *predictors* (a.k.a. *covariates*).

[1] https://dmrocke.ucdavis.edu/
[2] https://dmrocke.ucdavis.edu/Class/EPI204-Spring-2021/EPI204-Spring-2021.html
[3] https://www.bookdown.org/rwnahhas/RMPH/blr.html

Exercise 3.2 (Examples of binary outcomes)**.** What are some examples of binary outcomes in the health sciences?

Solution 3.2. Examples of binary outcomes include:

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

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

Exercise 3.3. Write down a mathematical definition of the Bernoulli distribution.

Solution 3.3. The **Bernoulli distribution** family for a random variable X is defined as:

$$\begin{aligned}\Pr(X = x) &= 1_{x \in \{0,1\}} \pi^x (1-\pi)^{1-x} \\ &= \begin{cases} \pi, x = 1 \\ 1 - \pi, x = 0 \end{cases}\end{aligned}$$

3.1.1. 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 3.4. Recall: what kinds of outcomes is linear regression used for?

Solution 3.4. 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:

- weight
- height
- income
- prices

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.

```
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 |> pander::pander()
```

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

OC	MI	No MI	Total
OC use	13	4,987	5,000
No OC use	7	9,993	10,000
Total	20	14,980	15,000

Exercise 3.5. Estimate the probabilities of MI for OC users and non-OC users in Example 3.1.

Solution 3.5.

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

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

Exercise 3.6. What does the term "controls" mean in the context of study design?

Solution 3.6.

Definition 3.2 (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.

Exercise 3.7. What types of studies do the two definitions of controls correspond to?

Solution 3.7.

Definition 3.3 (cases and controls in retrospective studies). In *retrospective case-control studies*, participants who experience the outcome of interest are called **cases**, while participants who don't experience that outcome are called **controls**.

Definition 3.4 (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 3.5 (Risk difference)**.** The **risk difference** of two probabilities, π_1, and π_2, is the difference of their values:

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

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:

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

Exercise 3.8 (interpreting risk differences)**.** How can we interpret the preceding relative risk estimate in prose?

Solution 3.8 (interpreting risk differences). "The difference in risk of MI between OC users and non-users was 0.0019."

or

"The difference in risk of MI between OC users and non-users was 0.19 percentage points[4]."

See the note about working with percentages in the Appendix.

---

[4] https://en.wikipedia.org/wiki/Percentage_point

3.3.2. Risk ratios

Exercise 3.9. If π_1 and π_2 are two probabilities, what do we call the following ratio?

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

Solution 3.9.

Definition 3.6 (Relative risk ratios). The ratio of two probabilities π_1 and π_2,

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

is called the:

- **risk ratio**,
- **relative risk ratio**,
- **probability ratio**,
- or **rate ratio**

of π_1 compared to π_2.

Exercise 3.10.

Above, we estimated that:

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

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

Now, estimate the *relative risk* of MI for OC versus non-OC.

Solution 3.10.

The *relative risk* of MI for OC versus non-OC is:

```
rr <- (13 / 5000) / (7 / 10000)
```

$$\begin{aligned}\hat{\rho}(OC, \neg OC) &= \frac{\hat{\mathrm{p}}(MI|OC)}{\hat{\mathrm{p}}(MI|\neg OC)} \\ &= \frac{0.0026}{7 \times 10^{-4}} \\ &= 3.714286\end{aligned}$$

Exercise 3.11. How can we interpret the preceding relative risk estimate in prose?

Solution 3.11.

We might summarize this result by saying that:

- "The estimated probability of MI among OC users was 3.714286 times as high as the estimated probability among OC non-users."

or

- "The estimated probability of MI among OC users was 2.714286 times higher than, the estimated probability among OC non-users."

see also Section 8.1.4[5] which uses similar phrasing.

3.3.3. Relative risk differences

The second approach above, where we subtract 1 from the risk ratio, is actually reporting a slightly different metric:

Definition 3.7 (Relative risk difference)**.**

Sometimes, we divide the risk difference by the comparison probability; the result is called the **relative risk difference**:

$$\xi(\pi_1, \pi_2) \stackrel{\text{def}}{=} \frac{\delta(\pi_1, \pi_2)}{\pi_2}$$

Theorem 3.1 (Relative risk difference equals risk ratio minus 1)**.**

$$\xi(\pi_1, \pi_2) = \rho(\pi_1, \pi_2) - 1$$

---

[5] https://link.springer.com/chapter/10.1007/978-1-4614-1353-0_8#Sec5_8

Proof.

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

□

3.3.4. 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).

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

$$\rho(\pi_2, \pi_1) = (\rho(\pi_1, \pi_2))^{-1}$$
$$\xi(\pi_2, \pi_1) = (\xi(\pi_1, \pi_2) + 1)^{-1} - 1$$

Exercise 3.12. Prove the relationships above.

Example 3.3 (Switching the reference group in a risk ratio)**.** Above, we estimated that the risk ratio of OC versus non-OC is:

$$\rho(OC, \neg OC) = 3.714286$$

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

$$\begin{aligned}\rho(\neg OC, OC) &= \frac{\hat{\mathrm{p}}(MI|\neg OC)}{\hat{\mathrm{p}}(MI|OC)} \\ &= \frac{7 \times 10^{-4}}{0.0026} \\ &= 0.269231 \\ &= \frac{1}{\rho(OC, \neg OC)}\end{aligned}$$

3.4. Odds and odds ratios

3.4.1. Odds and probabilities

In logistic regression, we will make use of a mathematically-convenient transformation of probability, called *odds*:

Definition 3.8 (Odds)**.**

The **odds** of an event A, is the probability that the event occurs, divided by the probability that it doesn't occur. We can represent odds with the Greek letter ω ("omega"). [6] Thus, in mathematical notation:

$$\omega \stackrel{\text{def}}{=} \frac{\Pr(A)}{\Pr(\neg A)} \tag{3.1}$$

This course is about regression models, which are conditional probability models (Definition 1.1). Accordingly, we define conditional odds in terms of conditional probabilities:

Definition 3.9 (Conditional odds)**.**

The **conditional odds** of an event A given a condition B, is the (conditional) probability that event A occurs (given condition B), divided by the (conditional) probability that it doesn't occur (given condition B). We can represent conditional odds using $\omega(A|B)$, $\omega(B)$ or ω_B ("omega bee"). Thus, in mathematical notation:

$$\omega(B) \stackrel{\text{def}}{=} \frac{\Pr(A|B)}{\Pr(\neg A|B)} \tag{3.2}$$

Example 3.4 (Computing odds from probabilities)**.** In Exercise 3.5, 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:

$$\begin{aligned}
\omega(OC) &\stackrel{\text{def}}{=} \frac{\Pr(MI|OC)}{\Pr(\neg MI|OC)} \\
&= \frac{\Pr(MI|OC)}{1 - \Pr(MI|OC)} \\
&= \frac{\pi(OC)}{1 - \pi(OC)} \\
&= \frac{0.0026}{1 - 0.0026} \\
&\approx 0.002607
\end{aligned}$$

[6] The name "omega" is a contraction of "o mega", which means "long o" in Greek, in contrast with "omicron" (o, "short o"). See https://www.etymonline.com/search?q=omega and https://en.wikipedia.org/wiki/Omega for more details.

Exercise 3.13 (Computing odds from probabilities)**.** Estimate the odds of MI, for non-OC users.

Solution.

$$\omega(\neg OC) = 7.004903 \times 10^{-4}$$

Exercise 3.14. Find a general formula for converting probabilities into odds.

Solution 3.12. Using Definition 3.8 and Corollary C.2:

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

Theorem 3.2. *If π is the probability of an event A and ω is the corresponding odds of A, then:*

$$\omega = \frac{\pi}{1-\pi} \tag{3.3}$$

Proof. By Solution 3.12. □

The mathematical relationship between odds ω and probabilities π, which is represented in Equation 3.3, is a core component of logistic regression models, as we will see in the rest of this chapter. Let's give the expression on the righthand side of Equation 3.3 its own name and symbol, so that we can refer to it concisely:

Definition 3.10 (Odds function)**.** The **odds function** is defined as:

$$\text{odds}\{\pi\} \stackrel{\text{def}}{=} \frac{\pi}{1-\pi} \tag{3.4}$$

We can use the odds function (Definition 3.10) to simplify Equation 3.3 (in Theorem 3.2) into a more concise expression, which is easier to remember and manipulate:

Corollary 3.1. *If π is the probability of an outcome A and ω is the corresponding odds of A, then:*

$$\omega = odds\{\pi\} \tag{3.5}$$

In other words, the odds function rescales probabilities into odds.

Proof. By Theorem 3.2 and Definition 3.10. □

Exercise 3.15. Graph the odds function.

Solution 3.13.

Figure 3.1 graphs the odds function.

```
odds <- function(pi) pi / (1 - pi)
library(ggplot2)
ggplot() +
  geom_function(
    fun = odds,
    arrow = arrow(ends = "last"),
    mapping = aes(col = "odds function")
  ) +
  xlim(0, .99) +
  xlab("Probability") +
  ylab("Odds") +
  geom_abline(aes(
    intercept = 0,
    slope = 1,
    col = "y=x"
  )) +
  theme_bw() +
  labs(colour = "") +
  theme(legend.position = "bottom")
```

Figure 3.1.: Odds versus probability

Theorem 3.3 (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.

$$\begin{aligned} 1 - \hat{\pi} &= 1 - \frac{x}{n} \\ &= \frac{n}{n} - \frac{x}{n} \\ &= \frac{n-x}{n} \end{aligned}$$

Thus, the estimated odds is:

$$\begin{aligned} \frac{\hat{\pi}}{1-\hat{\pi}} &= \frac{\left(\frac{x}{n}\right)}{\left(\frac{n-x}{n}\right)} \\ &= \frac{x}{n-x} \end{aligned} \tag{3.6}$$

That is, the odds estimate can be computed directly as "# events" divided by "# nonevents", without needing to compute $\hat{\pi}$ and $1 - \hat{\pi}$ first.

□

Example 3.5 (Calculating odds using the shortcut)**.** In Example 3.4, we calculated

$$\omega(OC) = 0.002607$$

Let's recalculate this result using our shortcut.

Solution 3.14.

$$\begin{aligned}\omega(OC) &= \frac{13}{5000-13} \\ &= 0.002607\end{aligned}$$

Same answer as in Example 3.4!

Theorem 3.4 (Simplified expressions for odds function)**.**

Two equivalent expressions for the odds function are:

$$\begin{aligned}odds\{\pi\} &= \frac{1}{\pi^{-1}-1} \\ &= \left(\pi^{-1}-1\right)^{-1}\end{aligned} \tag{3.7}$$

Exercise 3.16. Prove Theorem 3.4.

Solution 3.15. Starting from Definition 3.10:

$$\begin{aligned}\text{odds}\{\pi\} &= \frac{\pi}{1-\pi} \\ &= \frac{\pi}{1-\pi}\frac{\pi^{-1}}{\pi^{-1}} \\ &= \frac{\pi\pi^{-1}}{(1-\pi)\pi^{-1}} \\ &= \frac{1}{(\pi^{-1}-\pi\pi^{-1})} \\ &= \frac{1}{(\pi^{-1}-1)} \\ &= \left(\pi^{-1}-1\right)^{-1}\end{aligned}$$

Corollary 3.2 (Odds of a non-event)**.** *If π is the odds of event A and ω is the corresponding odds of A, then the odds of $\neg A$ are:*

$$\begin{aligned}\omega(\neg A) &= \frac{1-\pi}{\pi} \\ &= \pi^{-1} - 1\end{aligned}$$

Proof. Left to the reader. □

3.4.1.1. Odds of rare events

Exercise 3.17. What odds value corresponds to the probability $\pi = 0.2$, and what is the numerical difference between these two values?

Solution.

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

Exercise 3.18. Find the difference between an odds ω and its corresponding probability π, as a function of π.

Solution 3.16.

$$\begin{aligned}\omega - \pi &= \frac{\pi}{1-\pi} - \pi \\ &= \frac{\pi}{1-\pi} - \frac{\pi(1-\pi)}{1-\pi} \\ &= \frac{\pi}{1-\pi} - \frac{\pi - \pi^2}{1-\pi} \\ &= \frac{\pi - (\pi - \pi^2)}{1-\pi} \\ &= \frac{\pi - \pi + \pi^2}{1-\pi} \\ &= \frac{\pi^2}{1-\pi} \\ &= \frac{\pi}{1-\pi}\pi \\ &= \omega\pi\end{aligned}$$

Theorem 3.5. *Let* $\omega = \frac{\pi}{1-\pi}$. *Then:*

$$\omega - \pi = \frac{\pi^2}{1-\pi}$$

Proof. By Solution 3.16. □

For rare events (small π), odds and probabilities are nearly equal (see Figure 3.1), because $1 - \pi \approx 1$ and $\pi^2 \approx 0$.

For example, in Example 3.4, the probability and odds differ by 6.777622×10^{-6}.

3.4.2. The inverse odds function

Exercise 3.19. If π is the probability of an event A and ω is the corresponding odds of A, how can we compute π from ω?

For example, if $\omega = 3/2$, what is π?

Solution 3.17. Starting from Theorem 3.2, we can solve Equation 3.3 for π in terms of ω:

$$\begin{aligned}
\omega &= \frac{\pi}{1-\pi} \\
(1-\pi)\omega &= \pi \\
\omega - \pi\omega &= \pi \\
\omega &= \pi + \pi\omega \\
\omega &= (1+\omega)\pi \\
\pi &= \frac{\omega}{1+\omega}
\end{aligned}$$

So if $\omega = 3/2$,

$$\begin{aligned}
\pi &= \frac{3/2}{1+3/2} \\
&= \frac{3/2}{5/2} \\
&= \frac{3}{5}
\end{aligned}$$

Theorem 3.6. *If* π *is the probability of an event and* ω *is the corresponding odds of that event, then:*

$$\pi = \frac{\omega}{1+\omega} \tag{3.8}$$

Proof. By Theorem 3.2 and Solution 3.17. □

Definition 3.11 (inverse odds function)**.**

$$\text{invodds}\{\omega\} \stackrel{\text{def}}{=} \frac{\omega}{1+\omega} \tag{3.9}$$

can be called the **inverse-odds function**.

Corollary 3.3.

$$\pi = \mathit{invodds}\{\omega\}$$

Proof. By Definition 3.11 and Theorem 3.6. □

Corollary 3.4.

$$\mathit{invodds}\{\omega\} = \mathit{odds}^{-1}\{\omega\}$$

Proof. Using Corollary 3.1 and Theorem 3.6:

$$\begin{aligned}\text{invodds}\{\text{odds}\{\pi\}\} &= \text{invodds}\{\omega\} \\ &= \frac{\omega}{1+\omega} \\ &= \pi\end{aligned}$$

Likewise (not shown):

$$\text{odds}\{\text{invodds}\{\omega\}\} = \omega$$

□

The inverse-odds function converts odds into their corresponding probabilities (Figure 3.2). Its domain of inputs is $\omega \in [0, \infty)$ and its range of outputs is $\pi \in [0, 1]$.

I haven't seen anyone give the inverse-odds function a concise name; maybe prob() or prob() or risk()?

```
odds_inv <- function(omega) (1 + omega^-1)^-1
library(ggplot2)
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, invodds$\{\omega\}$

Exercise 3.20. What probability corresponds to an odds of $\omega = 1$, and what is the numerical difference between these two values?

Solution.

$$\begin{aligned}\pi &= \text{invodds}\{1\} \\ &= \frac{1}{1+1} \\ &= \frac{1}{2} \\ &= .5\end{aligned}$$

$$\begin{aligned}\omega - \pi &= 1 - .5 \\ &= .5\end{aligned}$$

Lemma 3.1 (Simplified expression for inverse odds function)**.**

Equivalent expressions for the inverse odds function are:

$$\begin{aligned}\mathit{invodds}\{\omega\} &= \frac{1}{1+\omega^{-1}} \\ &= (1+\omega^{-1})^{-1}\end{aligned} \tag{3.10}$$

Exercise 3.21. Prove that Equation 3.10 is equivalent to Definition 3.11.

Solution 3.18. Analogous to Solution 3.15.

Lemma 3.2 (One minus inverse-odds)**.**

$$1 - \pi = \frac{1}{1+\omega}$$

Proof. By Theorem 3.6:

$$\begin{aligned}1 - \pi &= 1 - \frac{\omega}{1+\omega} \\ &= \frac{1+\omega}{1+\omega} - \frac{\omega}{1+\omega} \\ &= \frac{(1+\omega) - \omega}{1+\omega} \\ &= \frac{1+\omega-\omega}{1+\omega} \\ &= \frac{1}{1+\omega}\end{aligned}$$

□

Corollary 3.5.

$$1 + \omega = \frac{1}{1-\pi}$$

3.4.3. Odds ratios

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

Definition 3.12 (Odds ratio)**.** The **odds ratio** for two conditional odds, ω_1 and ω_2, is the ratio of those odds:

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

There's a 1:1 mapping between probability and odds, and according to that mapping, the odds are equal between two covariate patterns IF and ONLY IF the probabilities are also equal between those patterns. So, testing whether an odds ratio = 1 is equivalent to testing whether the corresponding risk ratio = 1, and also equivalent to testing whether the risk difference = 0. Therefore, in **hypothesis testing**, if the null hypothesis is no effect, then we can shift between RD, RR, and OR. But when we're talking about **point estimates** and **CIs**, we need to limit our conclusions to the effect measure(s) that we actually estimated, because the *sizes* of RDs, RRs, and ORs don't have a simple relationship to each other, except when pi_1=pi_2 (as shown by Figure 3.3).

An *odds ratio* is a *ratio of odds*. An odds is a ratio of probabilities, so odds ratios are ratios of ratios:

Theorem 3.7.

$$\begin{aligned}\theta(\omega_1, \omega_2) &= \frac{\omega_1}{\omega_2} \\ &= \frac{\left(\frac{\pi_1}{1-\pi_1}\right)}{\left(\frac{\pi_2}{1-\pi_2}\right)}\end{aligned}$$

Example 3.6 (Calculating odds ratios)**.** In Example 3.1, the odds ratio for OC users versus OC-non-users is:

$$\begin{aligned}\theta(\omega(OC), \omega(\neg OC)) &= \frac{\omega(OC)}{\omega(\neg OC)} \\ &= \frac{0.0026}{7 \times 10^{-4}} \\ &= 3.714286\end{aligned}$$

3.4.3.1. 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	c	d	c+d
Total	a+c	b+d	a+b+c+d

From this table, we have:

- $\widehat{\pi}(Event|Exposed) = a/(a+b)$
- $\widehat{\pi}(\neg Event|Exposed) = b/(a+b)$
- $\widehat{\omega}(Event|Exposed) = \frac{\frac{a}{a+b}}{\frac{b}{a+b}} = \frac{a}{b}$
- $\widehat{\omega}(Event|\neg Exposed) = \frac{c}{d}$ (see Exercise 3.22)
- $\theta(Exposed, \neg Exposed) = \frac{\frac{a}{b}}{\frac{c}{d}} = \frac{ad}{bc}$

Exercise 3.22. Given Table 3.2, show that $\widehat{\omega}(Event|\neg Exposed) = \frac{c}{d}$.

3.4.3.2. Properties of odds ratios

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

Theorem 3.8 (Odds ratios are reversible)**.** *For any two events A, B:*

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

Proof.

$$
\begin{aligned}
\theta(A|B) &\stackrel{\text{def}}{=} \frac{\omega(A|B)}{\omega(A|\neg B)} \\
&= \frac{\left(\frac{\mathrm{p}(A|B)}{\mathrm{p}(\neg A|B)}\right)}{\left(\frac{\mathrm{p}(A|\neg B)}{\mathrm{p}(\neg A|\neg B)}\right)} \\
&= \left(\frac{\mathrm{p}(A|B)}{\mathrm{p}(\neg A|B)}\right)\left(\frac{\mathrm{p}(A|\neg B)}{\mathrm{p}(\neg A|\neg B)}\right)^{-1} \\
&= \left(\frac{\mathrm{p}(A|B)}{\mathrm{p}(\neg A|B)}\right)\left(\frac{\mathrm{p}(\neg A|\neg B)}{\mathrm{p}(A|\neg B)}\right) \\
&= \left(\frac{\mathrm{p}(A|B)}{\mathrm{p}(\neg A|B)} \cdot \frac{\mathrm{p}(B)}{\mathrm{p}(B)}\right)\left(\frac{\mathrm{p}(\neg A|\neg B)}{\mathrm{p}(A|\neg B)} \cdot \frac{\mathrm{p}(\neg B)}{\mathrm{p}(\neg B)}\right) \\
&= \left(\frac{\mathrm{p}(A,B)}{\mathrm{p}(\neg A,B)}\right)\left(\frac{\mathrm{p}(\neg A,\neg B)}{\mathrm{p}(A,\neg B)}\right) \\
&= \left(\frac{\mathrm{p}(B,A)}{\mathrm{p}(B,\neg A)}\right)\left(\frac{\mathrm{p}(\neg B,\neg A)}{\mathrm{p}(\neg B,A)}\right) \\
&= \left(\frac{\mathrm{p}(B,A)}{\mathrm{p}(\neg B,A)}\right)\left(\frac{\mathrm{p}(\neg B,\neg A)}{\mathrm{p}(B,\neg A)}\right) \\
&= [\text{reverse the preceding steps}] \\
&= \theta(B|A)
\end{aligned}
$$

□

Example 3.7. In Example 3.1, we have:

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

Exercise 3.23. For Table 3.2, show that $\hat{\theta}(Exposed, Unexposed) = \hat{\theta}(Event, \neg Event)$.

Conditional odds ratios have the same reversibility property:

Theorem 3.9 (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 3.8, inserting C into the conditions (RHS of |) of every expression. □

3.4.3.3. Odds Ratios vs Probability (Risk) Ratios

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.

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] 2.02041
```

Example 3.8. 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.

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
```

Figure 3.3 compares risk differences, risk ratios, and odds ratios as functions of the underlying probabilities being compared.

```r
if (run_graphs) {
  RD <- function(p1, p2) p2 - p1
  RR <- function(p1, p2) p2 / p1
  odds <- function(p) p / (1 - p)
  OR <- function(p1, p2) odds(p2) / odds(p1)
  OR_minus_RR <- function(p1, p2) OR(p2, p1) - RR(p2, p1)

  n_ticks <- 201
  probs <- seq(.001, .99, length.out = n_ticks)
  RD_mat <- outer(probs, probs, RD)
  RR_mat <- outer(probs, probs, RR)
  OR_mat <- outer(probs, probs, OR)

  opacity <- .3
  z_min <- -1
  z_max <- 5
  plotly::plot_ly(
    x = ~probs,
    y = ~probs
  ) |>
    plotly::add_surface(
      z = ~ t(RD_mat),
      contours = list(
        z = list(
          show = TRUE,
          start = -1,
          end = 1,
          size = .1
        )
      ),
      name = "Risk Difference",
      showscale = FALSE,
      opacity = opacity,
      colorscale = list(c(0, 1), c("green", "green"))
    ) |>
    plotly::add_surface(
      opacity = opacity,
      colorscale = list(c(0, 1), c("red", "red")),
      z = ~ t(RR_mat),
      contours = list(
        z = list(
          show = TRUE,
          start = z_min,
          end = z_max,
          size = .2
        )
      ),
      showscale = FALSE,
      name = "Risk Ratio"
    ) |>
    plotly::add_surface(
      opacity = opacity,
      colorscale = list(c(0, 1), c("blue", "blue")),
      z = ~ t(OR_mat),
      contours = list(
```

3.4.3.4. Odds Ratios in 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.

We can still 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 3.4.3.2:

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

Exercise 3.24. 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 3.6.

Solution.

```
tbl_oc_mi |> pander::pander()
```

Table 3.3.: Simulated data from study of oral contraceptive use and heart attack risk

OC	MI	No MI	Total
OC use	13	4,987	5,000
No OC use	7	9,993	10,000
Total	20	14,980	15,000

- $\omega(OC|MI) = P(OC|MI)/(1–P(OC|MI) = \frac{13}{7} = 1.857143$
- $\omega(OC|\neg MI) = P(OC|\neg MI)/(1–P(OC|\neg MI) = \frac{4987}{9993} = 0.499049$
- $\theta(OC, MI) = \frac{\omega(OC|MI)}{\omega(OC|\neg MI)} = \frac{13/7}{4987/9993} = 3.721361$

This is the same estimate we calculated in Example 3.6.

3.4.3.5. Odds Ratios in Cross-Sectional Studies

- If a cross-sectional study is a uniform probability sample of a population (which it rarely is), then we can estimate prevalence (sometimes called "prevalence risk" or just "risk") using standard methods (Lee 1994), and we can thus also estimate prevalence differences, prevalence ratios, and prevalence odds ratios comparing sub-populations.
- If the cross-sectional study is a stratified probability sample, then we can estimate prevalence, prevalence differences, prevalence ratios, and prevalence odds ratios using specialized methods for complex surveys (Lumley 2010).
- If the study has sampling biases that we cannot adjust for with survey weights, such as in a convenience sample, then we need to treat it in the same way as a case-control study, and we cannot validly estimate prevalence, prevalence differences, or prevalence ratios; we can only validly estimate prevalence *odds* ratios.

3.5. The logit and expit functions

3.5.1. The logit function

Definition 3.13 (log-odds)**.**

If ω is the odds of an event A, then the **log-odds** of A, which we will represent by η ("eta"), is the natural logarithm of the odds of A:

$$\eta \stackrel{\text{def}}{=} \log\{\omega\} \tag{3.11}$$

Theorem 3.10. *If π is the probability of an event A, ω is the corresponding odds of A, and η is the corresponding log-odds of A, then:*

$$\eta = log\left\{\frac{\pi}{1-\pi}\right\} \tag{3.12}$$

Proof. Apply Definition 3.13 and then Theorem 3.2. □

Definition 3.14 (logit function)**.**

The **logit function** of a probability π is the natural logarithm of the odds function of π:

$$\text{logit}(\pi) \stackrel{\text{def}}{=} \log\{\text{odds}\{\pi\}\}$$

The **logit function** is a composite function[7].

Exercise 3.25 (Compose the logit function)**.** Mathematically expand the definition of the logit function.

Solution 3.19 (Compose the logit function)*.*

Theorem 3.11 (Expanded expression for logit)*.*

$$logit(\pi) = log\left\{\frac{\pi}{1-\pi}\right\} \tag{3.13}$$

Proof. Apply Definition 3.14 and then Definition 3.8 (details left to the reader). □

Corollary 3.6. *If π is the probability of an event A and η is the corresponding log-odds of A, then:*

$$\eta = logit\{\pi\}$$

Proof. Apply Theorem 3.10 and Theorem 3.11. □

Figure 3.4 shows the shape of the logit() function.

[7] https://en.wikipedia.org/wiki/Function_composition

```
odds <- function(pi) pi / (1 - pi)

logit <- function(p) log(odds(p))

library(ggplot2)
logit_plot <-
  ggplot() +
  geom_function(
    fun = logit,
    arrow = arrow(ends = "both")
  ) +
  xlim(.001, .999) +
  ylab("logit(p)") +
  xlab("p") +
  theme_bw()
print(logit_plot)
```

Figure 3.4.: The logit function

3.5.2. The expit function

Lemma 3.3.

If ω is the odds of an event A and η is the corresponding log-odds of A, then:

$$\omega = exp\{\eta\}$$

Proof. Start from Definition 3.13 and solve for ω. □

Theorem 3.12.

If π is the probability of an event A, ω is the corresponding odds of A, and η is the corresponding log-odds of A, then:

$$\pi = \frac{exp\{\eta\}}{1 + exp\{\eta\}}$$

Proof. Apply Theorem 3.6 and then Lemma 3.3. □

Definition 3.15 (expit, logistic, inverse-logit)**.** The **expit function** of a log-odds η, also known as the **inverse-logit function** or **logistic function**, is the inverse-odds of the exponential of η:

$$\text{expit}(\eta) \stackrel{\text{def}}{=} \text{invodds}\{\exp\{\eta\}\}$$

Theorem 3.13 (Expressions for expit function)**.**

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

Proof. Apply definitions and Lemma 3.1. Details left to the reader. □

Theorem 3.14. *If π is the probability of an event A, ω is the corresponding odds of A, and η is the corresponding log-odds of A, then:*

$$\pi = expit\{\eta\}$$

Proof. Apply Theorem 3.12 and Theorem 3.13. □

Figure 3.5 graphs the expit function.

```
expit <- function(eta) {
  exp(eta) / (1 + exp(eta))
}
library(ggplot2)
expit_plot <-
  ggplot() +
  geom_function(
    fun = expit,
    arrow = arrow(ends = "both")
  ) +
  xlim(-8, 8) +
  ylim(0, 1) +
  ylab(expression(expit(eta))) +
  xlab(expression(eta)) +
  theme_bw()
print(expit_plot)
```

Figure 3.5.: The expit function

Theorem 3.15 (logit and expit are each others' inverses)**.**

$$logit\{expit\{\eta\}\} = \eta$$

$$expit\{logit\{\pi\}\} = \pi$$

Proof. Left to the reader. □

3.5.3. Diagram of expit and logit

$$\left[\pi \stackrel{\text{def}}{=} \Pr(Y=1|\tilde{X}=\tilde{x})\right] \underbrace{\overbrace{\underset{\frac{\omega}{1+\omega}}{\overset{\frac{\pi}{1-\pi}}{\rightleftarrows}} \left[\omega \stackrel{\text{def}}{=} \text{odds}(Y=1|\tilde{X}=\tilde{x})\right] \underset{\exp\{\eta\}}{\overset{\log\{\omega\}}{\rightleftarrows}}}^{\text{logit}(\pi)}}_{\text{expit}(\eta)} \left[\eta(\tilde{x}) \stackrel{\text{def}}{=} \text{log-odds}(Y=1|\tilde{X}=\tilde{x})\right]$$

Figure 3.6.: Diagram of logistic regression link and inverse link functions

3.6. Introduction to logistic regression

- In Example 3.1, we estimated the risk and the odds of MI for two groups, defined by oral contraceptive use.
- 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.

3.6.1. Independent binary outcomes - general

Exercise 3.26. Let $\tilde{y}$ represent a data set of mutually independent binary outcomes, each with a potentially different event probability π_i:

$$\tilde{y} = (y_1, ..., y_n)$$
$$y_i \sim_{\perp\!\!\!\perp} \text{Ber}(\pi_i)$$

Write the likelihood of $\tilde{y}$.

Solution 3.20.

$$
\begin{aligned}
\pi_i &\stackrel{\text{def}}{=} \mathrm{P}(Y_i = 1) \\
\mathrm{P}(Y_i = 0) &= 1 - \pi_i \\
\mathrm{P}(Y_i = y_i) &= \mathrm{P}(Y_i = 1)^{y_i}\mathrm{P}(Y_i = 0)^{1-y_i} \\
&= (\pi_i)^{y_i}(1-\pi_i)^{1-y_i} \\
\mathcal{L}_i(\pi_i) &\stackrel{\text{def}}{=} \mathrm{P}(Y_i = y_i) \\
\mathcal{L}(\tilde{\pi}) &\stackrel{\text{def}}{=} \mathrm{P}(Y_1 = y_1, \dots, Y_n = y_n) \\
&= \prod_{i=1}^{n} \mathrm{P}(Y_i = y_i) \\
&= \prod_{i=1}^{n} \mathcal{L}_i(\pi_i) \\
&= \prod_{i=1}^{n} (\pi_i)^{y_i}(1-\pi_i)^{1-y_i}
\end{aligned}
$$

Exercise 3.27. Write the log-likelihood of $\tilde{y}$.

Solution 3.21.

$$
\begin{aligned}
\ell(\tilde{\pi}) &\stackrel{\text{def}}{=} \log\{\mathcal{L}(\tilde{\pi})\} \\
&= \log\left\{\prod_{i=1}^{n} \mathcal{L}_i(\pi_i)\right\} \\
&= \sum_{i=1}^{n} \log\{\mathcal{L}_i(\pi_i)\} \\
&= \sum_{i=1}^{n} \ell_i(\pi_i) \\
\ell_i(\pi_i) &\stackrel{\text{def}}{=} \log\{\mathcal{L}_i(\pi_i)\} \\
&= y_i \log\{\pi_i\} + (1-y_i)\log\{1-\pi_i\}
\end{aligned}
$$

3.6.2. Modeling π_i as a function of X_i

If there are only a few distinct X_i values, we can model π_i separately for each value of X_i.

Otherwise, we need regression.

$$
\begin{aligned}
\pi(x) &\equiv \mathrm{E}(Y = 1 | X = x) \\
&= f(x^\top \beta)
\end{aligned}
$$

Typically, we use the expit inverse-link:

$$
\pi(\tilde{x}) = \mathrm{expit}(\tilde{x}'\beta) \tag{3.14}
$$

Table 3.4.: Mortality rates of adult flour beetles after five hours' exposure to gaseous carbon disulphide (Bliss 1935)

```
library(glmx)
library(dplyr)
data(BeetleMortality, package = "glmx")
beetles <- BeetleMortality |>
  mutate(
    pct = died / n,
    survived = n - died,
    dose_c = dose - mean(dose)
  )
beetles
#> # A tibble: 8 x 6
#>    dose  died     n   pct survived   dose_c
#>   <dbl> <int> <int> <dbl>    <int>    <dbl>
#> 1  1.69     6    59 0.102       53 -0.103
#> 2  1.72    13    60 0.217       47 -0.0692
#> 3  1.76    18    62 0.290       44 -0.0382
#> 4  1.78    28    56 0.5         28 -0.00923
#> 5  1.81    52    63 0.825       11  0.0179
#> 6  1.84    53    59 0.898        6  0.0435
#> 7  1.86    61    62 0.984        1  0.0676
#> 8  1.88    60    60 1            0  0.0905
```

3.6.3. Meet the beetles

```
library(ggplot2)
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 3.7.: Mortality rates of adult flour beetles after five hours' exposure to gaseous carbon disulphide (Bliss 1935)

3.6.4. Why don't we use linear regression?

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

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

3.6.5. Zoom out

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

Figure 3.9.: Mortality rates of adult flour beetles after five hours' exposure to gaseous carbon disulphide (Bliss 1935)

3.6.6. 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 3.10.: Mortality rates of adult flour beetles after five hours' exposure to gaseous carbon disulphide (Bliss 1935)

3.6.7. Logistic regression

```
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()
```

Figure 3.11.: Mortality rates of adult flour beetles after five hours' exposure to gaseous carbon disulphide (Bliss 1935).

3.6.8. 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)

3.6.9. Fitting and manipulating logistic regression models in R

Table 3.6.

```
fitted(beetles_glm_grouped)
#>        1        2        3        4        5        6        7        8
#> 0.058601 0.164028 0.362119 0.605315 0.795172 0.903236 0.955196 0.979049
predict(beetles_glm_grouped, type = "response")
#>        1        2        3        4        5        6        7        8
#> 0.058601 0.164028 0.362119 0.605315 0.795172 0.903236 0.955196 0.979049
```

```
library(glmx)
library(dplyr)
data(BeetleMortality)
beetles <- BeetleMortality |>
  mutate(
    pct = died / n,
    survived = n - died
  )

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

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

Table 3.5.: logistic regression model for beetles data with grouped (binomial) data

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

3.6.9.1. Fitted values

Fitted values are provided on the probability scale (Table 3.6)

3.6.9.2. Count scale

For grouped data, we can convert to the count scale by multiplying by the group size:

```
beetles$n * fitted(beetles_glm_grouped)
#>        1        2        3        4        5        6        7        8
#>  3.45746  9.84167 22.45138 33.89763 50.09582 53.29091 59.22216 58.74296
```

3.6.9.3. Logit scale

```
predict(beetles_glm_grouped, type = "link")
#>         1         2         3         4         5         6         7         8
#> -2.776615 -1.628559 -0.566179  0.427661  1.356386  2.233707  3.059622  3.844412
```

Converting between logit and probability scales works as expected:

```
predict(beetles_glm_grouped, type = "link") |> arm::invlogit()
#>        1        2        3        4        5        6        7        8
#> 0.058601 0.164028 0.362119 0.605315 0.795172 0.903236 0.955196 0.979049
predict(beetles_glm_grouped, type = "response")
#>        1        2        3        4        5        6        7        8
#> 0.058601 0.164028 0.362119 0.605315 0.795172 0.903236 0.955196 0.979049

predict(beetles_glm_grouped, type = "response") |> arm::logit()
#>         1         2         3         4         5         6         7         8
#> -2.776615 -1.628559 -0.566179  0.427661  1.356386  2.233707  3.059622  3.844412
predict(beetles_glm_grouped, type = "link")
#>         1         2         3         4         5         6         7         8
#> -2.776615 -1.628559 -0.566179  0.427661  1.356386  2.233707  3.059622  3.844412
```

`type = "terms"` is confusing, because the variables get centered:

```
predict(beetles_glm_grouped, type = "terms")
#>        dose
#> 1 -3.520419
#> 2 -2.372363
#> 3 -1.309983
#> 4 -0.316144
#> 5  0.612582
#> 6  1.489902
#> 7  2.315817
```

```
#> 8  3.100608
#> attr(,"constant")
#> [1] 0.743804
coef(beetles_glm_grouped)["dose"] * beetles$dose
#> [1] 57.9408 59.0889 60.1513 61.1451 62.0738 62.9512 63.7771 64.5619
```

We can construct the link-scale predictions from the terms:

```
terms_pred <- predict(beetles_glm_grouped, type = "terms")
terms_pred + attr(terms_pred, "constant")
#>        dose
#> 1 -2.776615
#> 2 -1.628559
#> 3 -0.566179
#> 4  0.427661
#> 5  1.356386
#> 6  2.233707
#> 7  3.059622
#> 8  3.844412
#> attr(,"constant")
#> [1] 0.743804
predict(beetles_glm_grouped, type = "link")
#>         1         2         3         4         5         6         7         8
#> -2.776615 -1.628559 -0.566179  0.427661  1.356386  2.233707  3.059622  3.844412
```

3.6.9.4. Individual observations

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

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

Table 3.7.: `beetles` data in long format

```
beetles_long
#> # A tibble: 481 x 7
#>     dose  died     n   pct survived dose_c outcome
#>    <dbl> <int> <int> <dbl>    <int>  <dbl>   <dbl>
#>  1  1.69     6    59 0.102       53 -0.103       1
#>  2  1.69     6    59 0.102       53 -0.103       1
#>  3  1.69     6    59 0.102       53 -0.103       1
#>  4  1.69     6    59 0.102       53 -0.103       1
#>  5  1.69     6    59 0.102       53 -0.103       1
#>  6  1.69     6    59 0.102       53 -0.103       1
#>  7  1.69     6    59 0.102       53 -0.103       0
#>  8  1.69     6    59 0.102       53 -0.103       0
#>  9  1.69     6    59 0.102       53 -0.103       0
#> 10  1.69     6    59 0.102       53 -0.103       0
#> # i 471 more rows
```

Table 3.8.: logistic regression model for beetles data with individual Bernoulli data

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

Exercise 3.28. Compare this model with the grouped-observations model (Table 3.5).

Solution 3.22.

They seem the same! But not quite:

```
logLik(beetles_glm_grouped)
#> 'log Lik.' -18.7151 (df=2)
logLik(beetles_glm_ungrouped)
#> 'log Lik.' -186.235 (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.

3.7. Derivatives of logistic regression functions

In order to interpret logistic regression models and find their MLEs, we will need to compute various derivatives. This section compiles some useful results.

3.7.1. Derivatives of odds function

Theorem 3.16 (Derivative of odds function)**.**

$$odds'\{\pi\} = \frac{\partial \omega}{\partial \pi} = \frac{1}{(1-\pi)^2}$$

Proof. We can use Theorem 3.2 and the quotient rule (Theorem B.26):

$$\begin{aligned}
\frac{\partial \omega}{\partial \pi} &= \frac{\partial}{\partial \pi}\left(\frac{\pi}{1-\pi}\right) \\
&= \frac{\frac{\partial}{\partial \pi}\pi}{1-\pi} - \left(\frac{\pi}{(1-\pi)^2} \cdot \frac{\partial}{\partial \pi}(1-\pi)\right) \\
&= \frac{1}{1-\pi} - \frac{\pi}{(1-\pi)^2} \cdot (-1) \\
&= \frac{1}{1-\pi} + \frac{\pi}{(1-\pi)^2} \\
&= \frac{1-\pi}{(1-\pi)^2} + \frac{\pi}{(1-\pi)^2} \\
&= \frac{1-\pi+\pi}{(1-\pi)^2} \\
&= \frac{1}{(1-\pi)^2}
\end{aligned}$$

□

Corollary 3.7.

$$\frac{\partial \omega}{\partial \pi} = (1+\omega)^2$$

Proof. By Theorem 3.16 and Corollary 3.5. □

3.7.2. Derivatives of inverse-odds function

Theorem 3.17 (Derivative of inverse odds function)**.**

$$invodds'\{\omega\} = \frac{\partial \pi}{\partial \omega} = (1-\pi)^2 = \frac{1}{(1+\omega)^2} \tag{3.15}$$

Proof. By Theorem 3.16 and Corollary 3.7.

Or for a direct approach, use the quotient rule (Theorem B.26) again:

$$\begin{aligned}
\frac{\partial \pi}{\partial \omega} &= \frac{\partial}{\partial \omega} \frac{\omega}{1+\omega} \\
&= \frac{\frac{\partial}{\partial \omega}\omega}{1+\omega} - \frac{\omega}{(1+\omega)^2} \cdot \frac{\partial}{\partial \omega}(1+\omega) \\
&= \frac{1}{1+\omega} - \frac{\omega}{(1+\omega)^2} \cdot 1 \\
&= \frac{1}{1+\omega} - \frac{\omega}{(1+\omega)^2} \\
&= \frac{1+\omega}{(1+\omega)^2} - \frac{\omega}{(1+\omega)^2} \\
&= \frac{1+\omega-\omega}{(1+\omega)^2} \\
&= \frac{1}{(1+\omega)^2}
\end{aligned}$$

□

3.7.3. Derivatives of logit function

Lemma 3.4 (Derivative of log-odds by odds)**.**

$$\frac{\partial \eta}{\partial \omega} = \omega^{-1}$$

Proof. Using Definition 3.13:

$$\begin{aligned}
\frac{\partial \eta}{\partial \omega} &= \frac{\partial}{\partial \omega} \log \omega \\
&= \omega^{-1}
\end{aligned}$$

□

Theorem 3.18 (Derivative of log-odds by odds)**.**

$$\frac{\partial \eta}{\partial \omega} = \frac{1-\pi}{\pi}$$

Proof. Using Theorem 3.2 and Lemma 3.4:

$$\begin{aligned}\frac{\partial \eta}{\partial \omega} &= \omega^{-1} \\ &= \frac{1-\pi}{\pi}\end{aligned}$$

□

Theorem 3.19 (Derivative of log-odds by probability)**.**

$$\frac{\partial \eta}{\partial \pi} = \frac{1}{(\pi)(1-\pi)}$$

Proof. Using Theorem 3.18, Theorem 3.16, and the chain rule (Theorem B.27):

$$\begin{aligned}\frac{\partial \eta}{\partial \pi} &= \frac{\partial \eta}{\partial \omega}\frac{\partial \omega}{\partial \pi} \\ &= \frac{1-\pi}{\pi}\frac{1}{(1-\pi)^2} \\ &= \frac{1}{(\pi)(1-\pi)}\end{aligned}$$

□

Corollary 3.8 (Derivative of logit function)**.**

$$logit'(\pi) = \frac{1}{(\pi)(1-\pi)}$$

Proof. By Theorem 3.19 and Corollary 3.6. □

3.7.4. Derivatives of expit function

Lemma 3.5.

$$\frac{\partial \omega}{\partial \eta} = \omega$$

Proof. Using Lemma 3.3 and Theorem B.24:

$$\begin{aligned}\frac{\partial \omega}{\partial \eta} &= \frac{\partial}{\partial \eta}\exp\{\eta\} \\ &= \exp\{\eta\} \\ &= \omega\end{aligned}$$

□

Theorem 3.20.

$$\frac{\partial \omega}{\partial \eta} = \frac{\pi}{1-\pi} \tag{3.16}$$

Proof. Use Lemma 3.5 and Theorem 3.2. □

Theorem 3.21.

$$\frac{\partial \pi}{\partial \eta} = \pi(1-\pi)$$

Proof. By the chain rule (Theorem B.27), Theorem 3.20, and Theorem 3.17:

$$\begin{aligned}\frac{\partial \pi}{\partial \eta} &= \frac{\partial \omega}{\partial \eta}\frac{\partial \pi}{\partial \omega} \\ &= \frac{\pi}{1-\pi}(1-\pi)^2 \\ &= \pi(1-\pi)\end{aligned}$$

Alternatively, by Theorem 3.19:

$$\begin{aligned}\frac{\partial \pi}{\partial \eta} &= \left(\frac{\partial \eta}{\partial \pi}\right)^{-1} \\ &= \left(\frac{1}{(\pi)(1-\pi)}\right)^{-1} \\ &= \pi(1-\pi)\end{aligned}$$

□

Corollary 3.9. *If* $\pi = \Pr(Y = 1|\tilde{X} = \tilde{x})$*, then:*

$$\frac{\partial \pi}{\partial \eta} = Var(Y|X = x)$$

3.8. Understanding logistic regression models

Lemma 3.6. *By Theorem B.31:*

$$\begin{aligned}\frac{\partial \eta}{\partial \tilde{x}} &= \frac{\partial}{\partial \tilde{x}} \tilde{x} \cdot \tilde{\beta} \\ &= \tilde{\beta}\end{aligned}$$

Exercise 3.29. Consider a logistic regression model with a single predictor, X:

$$\begin{aligned} Y_i|X_i &\sim_{\perp\!\!\!\perp} \text{Ber}(\pi(X_i)) \\ \pi(x) &= \text{expit}\{\eta(x)\} = \pi(\omega(\eta(x))) \\ \eta(x) &= \alpha + \beta x \end{aligned} \tag{3.17}$$

Find the derivative of $\pi(x) = \text{E}[Y|X = x]$ with respect to x:

$$\frac{\partial \pi}{\partial x} = ?$$

Solution 3.23. By Theorem 3.21, Lemma 3.6, and the chain rule (Theorem B.27):

$$\begin{aligned}\frac{\partial \pi}{\partial x} &= \frac{\partial \pi}{\partial \eta}\frac{\partial \eta}{\partial x} \\ &= \pi(1-\pi)\beta \\ &= \text{Var}(Y|X = x) \cdot \beta\end{aligned}$$

The slope is steepest at $\pi = 0.5$, i.e., at $\eta = 0$, which for a unipredictor model occurs at $x = -\alpha/\beta$. The slope goes to 0 as x goes to $-\infty$ or $+\infty$ (compare with Figure 3.5).

Note

In order to interpret β_j: differentiate or difference $\eta(\tilde{x})$ with respect to x_j (depending on whether x_j is continuous or discrete, respectively):

$$\frac{\partial}{\partial x_j}\eta(\tilde{x})$$

In order to find the MLE $\hat{\tilde{\beta}}$: differentiate the log-likelihood function $\ell(\tilde{\beta})$ with respect to $\tilde{\beta}$:

$$\frac{\partial}{\partial \tilde{\beta}}\ell(\tilde{\beta})$$

Exercise 3.30 (General formula for odds ratios in logistic regression)**.** Consider the generic logistic regression model:

- $Y_i|\tilde{X}_i \sim_{\perp\!\!\!\perp} \text{Ber}(\pi(\tilde{X}_i))$
- $\text{logit}\{\pi(\tilde{x})\} = \eta(\tilde{x})$
- $\eta(\tilde{x}) = \tilde{x}'\tilde{\beta}$

Let $\tilde{x}$ and $\tilde{x}^*$ be two covariate patterns, representing two individuals or two subpopulations.

Find a concise formula to compute the odds ratio comparing covariate patterns $\tilde{x}$ and $\tilde{x}^*$:

$$\theta(\tilde{x}, \tilde{x}^*) \stackrel{\text{def}}{=} \frac{\omega(\tilde{x})}{\omega(\tilde{x}^*)} \tag{3.18}$$

Solution 3.24 (General formula for odds ratios in logistic regression).

$$\begin{aligned}\theta(\tilde{x}, \tilde{x}^*) &\stackrel{\text{def}}{=} \frac{\omega(\tilde{x})}{\omega(\tilde{x}^*)} \\ &= \frac{\exp\{\eta(\tilde{x})\}}{\exp\{\eta(\tilde{x}^*)\}} \\ &= \exp\{\eta(\tilde{x}) - \eta(\tilde{x}^*)\}\end{aligned}$$

Solution 3.24 is more concrete than Equation 3.18, but it doesn't yet completely explain how to compute $\theta(\tilde{x}, \tilde{x}^*)$, so let's mark it as a lemma:

Lemma 3.7 (General formula for odds ratios in logistic regression)**.**

$$\theta(\tilde{x}, \tilde{x}^*) = exp\{\eta(\tilde{x}) - \eta(\tilde{x}^*)\} \tag{3.19}$$

Proof. By Solution 3.24. □

Definition 3.16 (Difference in log-odds)**.**

Let $\tilde{x}$ and $\tilde{x}^*$ be two covariate patterns, representing two individuals or two subpopulations.

Then we can define the difference in log-odds between $\tilde{x}$ and $\tilde{x}^*$, denoted $\Delta\eta(\tilde{x}, \tilde{x}^*)$ or $\Delta\eta$ for short, as:

$$\Delta\eta \stackrel{\text{def}}{=} \eta(\tilde{x}) - \eta(\tilde{x}^*)$$

Corollary 3.10 (Shorthand general formula for odds ratios in logistic regression)**.**

$$\theta(\tilde{x}, \tilde{x}^*) = exp\{\Delta\eta\} \tag{3.20}$$

Proof. By Lemma 3.7 and Definition 3.16. □

Exercise 3.31 (Difference in log-odds)**.** Find a concise expression for the difference in log-odds:

$$\Delta\eta \stackrel{\text{def}}{=} \eta(\tilde{x}) - \eta(\tilde{x}^*)$$

Solution 3.25 (Difference in log-odds).

$$\begin{aligned}
\Delta\eta &\stackrel{\text{def}}{=} \eta(\tilde{x}) - \eta(\tilde{x}^*) \\
&= (\tilde{x} \cdot \tilde{\beta}) - (\tilde{x}^* \cdot \tilde{\beta}) \\
&= (\tilde{x}^\top \tilde{\beta}) - ((\tilde{x}^*)^\top \tilde{\beta}) \\
&= (\tilde{x}^\top - (\tilde{x}^*)^\top)\tilde{\beta} \\
&= (\tilde{x} - \tilde{x}^*)^\top \tilde{\beta} \\
&= (\tilde{x} - \tilde{x}^*) \cdot \tilde{\beta}
\end{aligned}$$

Lemma 3.8 (Difference in log-odds)**.**

$$\Delta\eta = (\tilde{x} - \tilde{x}^*) \cdot \tilde{\beta}$$

Proof. By Solution 3.25. □

Definition 3.17 (Difference in covariate patterns)**.**

Let $\tilde{x}$ and $\tilde{x}^*$ be two covariate patterns, representing two individuals or two subpopulations. The difference in covariate patterns, denoted $\Delta\tilde{x}$, is defined as:

$$\Delta\tilde{x} \stackrel{\text{def}}{=} \tilde{x} - \tilde{x}^*$$

Corollary 3.11 (Difference in log-odds)**.**

$$\Delta\eta = (\Delta\tilde{x}) \cdot \tilde{\beta}$$

Proof. By Lemma 3.8 and Definition 3.17. □

Exercise 3.32. Find an expression for the odds ratio $\theta(\tilde{x}, \tilde{x}^*)$ in terms of $\Delta\tilde{x}$ and $\tilde{\beta}$.

Solution 3.26. Combine Corollary 3.10 and Corollary 3.11:

$$\begin{aligned}\theta(\tilde{x}, \tilde{x}^*) &= \exp\{\Delta\eta\} \\ &= \exp\Big\{\Delta\tilde{x} \cdot \tilde{\beta}\Big\}\end{aligned}$$

Theorem 3.22. *The odds ratio comparing covariate patterns $\tilde{x}$ and $\tilde{x}^*$ is:*

$$\theta(\tilde{x}, \tilde{x}^*) = exp\Big\{(\Delta\tilde{x}) \cdot \tilde{\beta}\Big\} \tag{3.21}$$

Proof. By Solution 3.26. □

Corollary 3.12.

$$log\{\theta(\tilde{x}, \tilde{x}^*)\} = \Delta\eta$$

3.9. Estimating logistic regression models

3.9.1. Model

Assume:

- $Y_i|\tilde{X}_i \sim_{\perp\!\!\!\perp} \text{Ber}(\pi(X_i))$
- $\pi(\tilde{x}) = \text{expit}\{\eta(\tilde{x})\}$
- $\eta(\tilde{x}) = \tilde{x} \cdot \tilde{\beta}$

Table 3.9.: Mortality rates of adult flour beetles after five hours' exposure to gaseous carbon disulphide (Bliss 1935)

```
library(glmx)
library(dplyr)
data(BeetleMortality)
beetles <- BeetleMortality |>
  mutate(
    pct = died / n,
    survived = n - died,
    dose_c = dose - mean(dose)
  )
beetles_long <-
  beetles |>
  reframe(
    .by = everything(),
    outcome = c(
      rep(1, times = died),
      rep(0, times = survived)
    )
  )
beetles
#> # A tibble: 8 x 6
#>    dose  died     n   pct survived   dose_c
#>   <dbl> <int> <int> <dbl>    <int>    <dbl>
#> 1  1.69     6    59 0.102       53 -0.103
#> 2  1.72    13    60 0.217       47 -0.0692
#> 3  1.76    18    62 0.290       44 -0.0382
#> 4  1.78    28    56 0.5         28 -0.00923
#> 5  1.81    52    63 0.825       11  0.0179
#> 6  1.84    53    59 0.898        6  0.0435
#> 7  1.86    61    62 0.984        1  0.0676
#> 8  1.88    60    60 1            0  0.0905
```

3.9.2. Likelihood function

Exercise 3.33. Compute and graph the likelihood for the `beetles` data model:

```
beetles_glm <-
  beetles |>
  glm(
    formula = cbind(died, survived) ~ dose,
    family = "binomial"
  )
equatiomatic::extract_eq(beetles_glm)
```

$$\log\left[\frac{P(\text{died} = 60)}{1 - P(\text{died} = 60)}\right] = \alpha + \beta_1(\text{dose}) \tag{3.22}$$

```r
beetles_glm |>
  parameters::parameters() |>
  parameters::print_md()
```

Table 3.10.: Fitted logistic regression model for `beetles` data

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

Solution 3.27.

```r
odds_inv <- function(omega) (1 + omega^-1)^-1
lik_beetles0 <- function(beta_0, beta_1) {
  beetles |>
    mutate(
      eta = beta_0 + beta_1 * dose,
      omega = exp(eta),
      pi = odds_inv(omega),
      Lik = pi^died * (1 - pi)^survived,
      # llik = died*eta + n*log(1 - pi)
    ) |>
    pull(Lik) |>
    prod()
}

lik_beetles <- Vectorize(lik_beetles0)
```

3.9.3. Log-likelihood function

Exercise 3.34. Find the log-likelihood function for the general logistic regression model.

Solution 3.28.

$$\begin{aligned} \ell(\tilde{\beta}, \tilde{y}) &= \log\Big\{\mathcal{L}(\tilde{\beta}, \tilde{y})\Big\} \\ &= \sum_{i=1}^{n} \ell_i(\pi(\tilde{x}_i)) \end{aligned} \tag{3.23}$$

Using Theorem 3.10 and Corollary 3.5:

$$
\begin{aligned}
\ell_i(\pi_i) &= y_i \log\{\pi_i\} + (1 - y_i)\log\{1 - \pi_i\} \\
&= y_i \log\{\pi_i\} + (1 \cdot \log\{1 - \pi_i\} - y_i \cdot \log\{1 - \pi_i\}) \\
&= y_i \log\{\pi_i\} + (\log\{1 - \pi_i\} - y_i \log\{1 - \pi_i\}) \\
&= y_i \log\{\pi_i\} + \log\{1 - \pi_i\} - y_i \log\{1 - \pi_i\} \\
&= y_i \log\{\pi_i\} - y_i \log\{1 - \pi_i\} + \log\{1 - \pi_i\} \\
&= (y_i \log\{\pi_i\} - y_i \log\{1 - \pi_i\}) + \log\{1 - \pi_i\} \\
&= y_i (\log\{\pi_i\} - \log\{1 - \pi_i\}) + \log\{1 - \pi_i\} \\
&= y_i \left(\log\left\{ \frac{\pi_i}{1 - \pi_i} \right\} \right) + \log\{1 - \pi_i\} \\
&= y_i \text{logit}(\pi_i) + \log\{1 - \pi_i\} \\
&= y_i \eta_i + \log\{1 - \pi_i\} \\
&= y_i \eta_i + \log\left\{ (1 + \omega_i)^{-1} \right\} \\
&= y_i \eta_i - \log\{1 + \omega_i\}
\end{aligned}
$$

Lemma 3.9.

$$\ell_i(\pi_i) = y_i \eta_i - log\{1 + \omega_i\}$$

Exercise 3.35. Compute and graph the log-likelihood for the `beetles` data.

Solution 3.29.

```
odds_inv <- function(omega) (1 + omega^-1)^-1
llik_beetles0 <- function(beta_0, beta_1) {
  beetles |>
    mutate(
      eta = beta_0 + beta_1 * dose,
      omega = exp(eta),
      pi = odds_inv(omega), # need for next line:
      llik = died*eta + n*log(1 - pi)
    ) |>
    pull(llik) |>
    sum()
}

llik_beetles <- Vectorize(llik_beetles0)

# to check that we implemented it correctly:
# ests = coef(beetles_glm_ungrouped)
# logLik(beetles_glm_ungrouped)
# llik_beetles(ests[1], ests[2])
```

Let's center dose:

```
beetles_glm_grouped_centered <- beetles |>
  glm(
    formula = cbind(died, survived) ~ dose_c,
    family = "binomial"
  )

beetles_glm_ungrouped_centered <- beetles_long |>
  mutate(died = outcome) |>
  glm(
    formula = died ~ dose_c,
    family = "binomial"
  )

equatiomatic::extract_eq(beetles_glm_ungrouped_centered)
```

$$\log\left[\frac{P(\text{died}=1)}{1-P(\text{died}=1)}\right] = \alpha + \beta_1(\text{dose_c}) \tag{3.24}$$

```
beetles_glm_grouped_centered |>
  parameters::parameters() |>
  parameters::print_md()
```

Table 3.11.: Fitted logistic regression model for `beetles` data, with `dose` centered

Parameter	Log-Odds	SE	95% CI	z	p
(Intercept)	0.74	0.14	(0.48, 1.02)	5.40	< .001
dose c	34.27	2.91	(28.85, 40.30)	11.77	< .001

```
odds_inv <- function(omega) (1 + omega^-1)^-1
lik_beetles0 <- function(beta_0, beta_1) {
  beetles |>
    mutate(
      eta = beta_0 + beta_1 * dose_c,
      omega = exp(eta),
      pi = odds_inv(omega),
      Lik = (pi^died) * (1 - pi)^(survived)
    ) |>
    pull(Lik) |>
    prod()
}

lik_beetles <- Vectorize(lik_beetles0)
```

```r
odds_inv <- function(omega) (1 + omega^-1)^-1
llik_beetles0 <- function(beta_0, beta_1) {
  beetles |>
    mutate(
      eta = beta_0 + beta_1 * dose_c,
      omega = exp(eta),
      pi = odds_inv(omega),
      llik = died * eta + n*log(1 - pi)
    ) |>
    pull(llik) |>
    sum()
}

llik_beetles <- Vectorize(llik_beetles0)
```

3.9.4. Score function

As usual, by independence, we have:

Lemma 3.10.

$$\begin{aligned}
\tilde{\ell}'(\tilde{\beta}) &\stackrel{def}{=} \frac{\partial}{\partial\tilde{\beta}}\ell(\tilde{\beta}) \\
&= \frac{\partial}{\partial\tilde{\beta}}\sum_{i=1}^{n}\ell_i(\tilde{\beta}) \\
&= \sum_{i=1}^{n}\frac{\partial}{\partial\tilde{\beta}}\ell_i(\tilde{\beta}) \\
&= \sum_{i=1}^{n}\tilde{\ell}_i'(\tilde{\beta})
\end{aligned}$$

Starting from Lemma 3.9, we can apply the vector chain rule (Theorem B.33):

Lemma 3.11.

$$\begin{aligned}
\tilde{\ell}_i'(\tilde{\beta}) &= \frac{\partial}{\partial\tilde{\beta}}\ell_i(\tilde{\beta}) \\
&= \frac{\partial}{\partial\tilde{\beta}}(y_i\eta_i - log\{1+\omega_i\}) \\
&= \frac{\partial}{\partial\tilde{\beta}}y_i\eta_i - \frac{\partial}{\partial\tilde{\beta}}log\{1+\omega_i\} \\
&= \frac{\partial\eta_i}{\partial\tilde{\beta}}y_i - \frac{\partial\omega_i}{\partial\tilde{\beta}}\frac{1}{1+\omega_i}
\end{aligned}$$

Lemma 3.12. *By Theorem B.31:*

$$\begin{aligned}\frac{\partial \eta}{\partial \tilde{\beta}} &= \frac{\partial}{\partial \tilde{\beta}}(\tilde{x} \cdot \tilde{\beta}) \\ &= \tilde{x}\end{aligned} \tag{3.25}$$

Lemma 3.12 is very similar to Lemma 3.6, but not quite the same; Lemma 3.6 differentiates by $\tilde{x}$, whereas Lemma 3.12 differentiates by $\tilde{\beta}$.

Theorem 3.23.

To derive $\frac{\partial \omega}{\partial \tilde{\beta}}$, we can apply the vector chain rule (Theorem B.33) again along with Lemma 3.5 and Lemma 3.12:

$$\begin{aligned}\frac{\partial \omega}{\partial \tilde{\beta}} &= \frac{\partial \eta}{\partial \tilde{\beta}} \frac{\partial \omega}{\partial \eta} \\ &= \tilde{x}\omega\end{aligned}$$

Corollary 3.13.

$$\frac{\partial \omega}{\partial \tilde{\beta}} = \tilde{x}\frac{\pi}{1-\pi}$$

Now we can combine Lemma 3.11, Lemma 3.12, and Theorem 3.23:

$$\begin{aligned}\ell_i'(\tilde{\beta}) &= \frac{\partial \eta_i}{\partial \tilde{\beta}} y_i - \frac{\partial \omega_i}{\partial \tilde{\beta}} \frac{1}{1+\omega_i} \\ &= \tilde{x}_i y_i - \tilde{x}\omega_i \frac{1}{1+\omega_i} \\ &= \tilde{x}_i y_i - \tilde{x}\frac{\omega_i}{1+\omega_i} \\ &= \tilde{x}_i y_i - \tilde{x}_i \pi_i \\ &= \tilde{x}_i (y_i - \pi_i) \\ &= \tilde{x}_i (y_i - \mu_i) \\ &= \tilde{x}_i (y_i - \mathrm{E}[Y_i | \tilde{X}_i = \tilde{x}_i]) \\ &= \tilde{x}_i \ \varepsilon(y_i | \tilde{X}_i = \tilde{x}_i) \\ &= \tilde{x}_i \varepsilon_i\end{aligned}$$

Theorem 3.24.

$$\ell_i'(\tilde{\beta}) = \tilde{x}_i \varepsilon_i \tag{3.26}$$

This last expression is essentially the same as we found in linear regression.

Finally, combining Lemma 3.10 and Theorem 3.24, we have:

Theorem 3.25.

$$\begin{aligned}\tilde{\ell}'(\tilde{\beta}) &= \sum_{i=1}^{n} \ell_i'(\tilde{\beta}) \\ &= \sum_{i=1}^{n} \tilde{x}_i \varepsilon_i \\ &= \mathbf{X}^\top \tilde{\varepsilon}\end{aligned} \tag{3.27}$$

The score function is vector-valued; its components are:

$$\frac{\partial \ell}{\partial \tilde{\beta}} = \begin{pmatrix} \frac{\partial \ell}{\partial \beta_0} \\ \frac{\partial \ell}{\partial \beta_1} \\ \vdots \\ \frac{\partial \ell}{\partial \beta_p} \end{pmatrix} = \begin{pmatrix} \sum_{i=1}^{n} 1\varepsilon_i \\ \sum_{i=1}^{n} x_{i,1}\varepsilon_i \\ \vdots \\ \sum_{i=1}^{n} x_{i,p}\varepsilon_i \end{pmatrix} = \begin{pmatrix} \tilde{1} \cdot \tilde{\varepsilon} \\ \tilde{x}_1 \cdot \tilde{\varepsilon} \\ \vdots \\ \tilde{x}_p \cdot \tilde{\varepsilon} \end{pmatrix}$$

Thus, the score equation $\tilde{\ell}' = 0$ means that for the MLE $\hat{\tilde{\beta}}$:

1. the sum of the errors (aka deviations) equals 0:

$$\sum_{i=1}^{n} \varepsilon_i = 0$$

2. the sums of the errors times each covariate also equal 0:

$$\tilde{x}_j \cdot \tilde{\varepsilon} = \sum_{i=1}^{n} x_{ij}\varepsilon_i = 0, \forall j \in \{1 : p\}$$

Example 3.9. In our model for the `beetles` data, we only have an intercept plus one covariate, gas concentration (c):

$$\tilde{x} = (1, c)$$

If c_i is the gas concentration for the beetle in observation i, and $\tilde{c} = (c_1, c_2, ...c_n)$, then the score equation $\tilde{\ell}' = 0$ means that for the MLE $\hat{\tilde{\beta}}$:

1. the sum of the errors (aka deviations) equals 0:

$$\sum_{i=1}^{n} \varepsilon_i = 0$$

2. the weighted sum of the error times the gas concentrations equals 0:

$$\sum_{i=1}^{n} c_i\varepsilon_i = 0$$

Exercise 3.36. Implement and graph the score function for the beetles data

---

Solution 3.30.

```
odds_inv <- function(omega) (1 + omega^-1)^-1

score_fn_beetles_beta0_0 <- function(beta_0, beta_1) {
  beetles |>
    mutate(
      eta = beta_0 + beta_1 * dose_c,
      omega = exp(eta),
      pi = odds_inv(omega),
      mu = pi * n,
      epsilon = died - mu,
      score = epsilon
    ) |>
    pull(score) |>
    sum()
}
score_fn_beetles_beta_0 <- Vectorize(score_fn_beetles_beta0_0)

score_fn_beetles_beta1_0 <- function(beta_0, beta_1) {
  beetles |>
    mutate(
      eta = beta_0 + beta_1 * dose_c,
      omega = exp(eta),
      pi = odds_inv(omega),
      mu = pi * n,
      epsilon = died - mu,
      score = dose_c * epsilon
    ) |>
    pull(score) |>
    sum()
}
score_fn_beetles_beta_1 <- Vectorize(score_fn_beetles_beta1_0)
```

3.9.5. Hessian function

$$\ell''(\tilde{\beta}) = \sum_{i=1}^{n} \ell_i''(\tilde{\beta}) \tag{3.28}$$

$$
\begin{aligned}
\ell_i''(\tilde{\beta}) &= \frac{\partial}{\partial \tilde{\beta}^\top} \tilde{\ell}_i' \\
&= \frac{\partial}{\partial \tilde{\beta}^\top} \tilde{x}_i \varepsilon_i \\
&= \tilde{x}_i \frac{\partial}{\partial \tilde{\beta}^\top} \varepsilon_i \\
&= \tilde{x}_i \varepsilon_i'
\end{aligned}
\tag{3.29}
$$

Theorem 3.26. *Using Lemma 3.12 and Theorem 3.21:*

$$
\begin{aligned}
\frac{\partial \pi}{\partial \tilde{\beta}} &= \frac{\partial \eta}{\partial \tilde{\beta}} \frac{\partial \pi}{\partial \eta} \\
&= \tilde{x} \pi (1 - \pi)
\end{aligned}
$$

Using Theorem 3.26:

$$
\begin{aligned}
\varepsilon_i' &= \frac{\partial \varepsilon_i}{\partial \tilde{\beta}^\top} \\
&= \frac{\partial}{\partial \tilde{\beta}^\top} \varepsilon_i \\
&= \frac{\partial}{\partial \tilde{\beta}^\top} (y_i - \mu_i) \\
&= \frac{\partial}{\partial \tilde{\beta}^\top} y_i - \frac{\partial}{\partial \tilde{\beta}^\top} \mu_i \\
&= 0 - \frac{\partial}{\partial \tilde{\beta}^\top} \mu_i \\
&= -\frac{\partial \mu_i}{\partial \tilde{\beta}^\top} \\
&= -\frac{\partial \pi_i}{\partial \tilde{\beta}^\top} \\
&= -\pi_i (1 - \pi_i) \tilde{x}_i^\top \\
&= -\mathrm{Var}(Y_i | X_i = x_i) \tilde{x}_i^\top
\end{aligned}
$$

Returning to Equation 3.29:

$$
\begin{aligned}
\ell_i''(\tilde{\beta}) &= \tilde{x}_i \varepsilon_i' \\
&= -\tilde{x}_i \mathrm{Var}(Y_i | X_i = x_i) \tilde{x}_i^\top
\end{aligned}
\tag{3.30}
$$

Returning to Equation 3.28:

$$\begin{aligned}\ell''(\tilde{\beta}) &= \sum_{i=1}^{n} \ell_i''(\tilde{\beta}) \\ &= -\sum_{i=1}^{n} \tilde{x}_i \mathrm{Var}(Y_i|X_i = x_i)\tilde{x}_i' \\ &= -\mathbf{X}^\top \mathbf{D}\mathbf{X}\end{aligned} \tag{3.31}$$

where $\mathbf{D} \stackrel{\text{def}}{=} \mathrm{diag}(\mathrm{Var}(Y_i|X_i = x_i))$ is the diagonal matrix whose i^{th} diagonal element is $\mathrm{Var}(Y_i|X_i = x_i)$.

Compare with Equation 2.6 from linear regression:

$$\begin{aligned}\ell''(\tilde{\beta}) &= -\frac{1}{\sigma^2}\sum_{i=1}^{n} \tilde{x}_i \tilde{x}_i' \\ &= -\mathbf{X}^\top \mathbf{D}^{-1}\mathbf{X}\end{aligned} \tag{3.32}$$

Exercise 3.37. Determine the elements of the Hessian matrix for logistic regression.

Solution 3.31. The components of the Hessian are:

$$\begin{aligned}\ell''(\beta) &= \frac{\partial^2}{\partial \beta^\top \partial \beta}\ell \\ &= \frac{\partial}{\partial \beta^\top}\ell' \\ &= \begin{bmatrix} \frac{\partial \ell'}{\partial \beta_0} & \frac{\partial \ell'}{\partial \beta_1} & \cdots & \frac{\partial \ell'}{\partial \beta_p} \end{bmatrix} \\ &= \begin{bmatrix} \frac{\partial^2 \ell}{\partial \beta_0^2} & \frac{\partial^2 \ell}{\partial \beta_0 \partial \beta_1} & \cdots & \frac{\partial^2 \ell}{\partial \beta_0 \partial \beta_p} \\ \frac{\partial^2 \ell}{\partial \beta_1 \partial \beta_0} & \frac{\partial^2 \ell}{\partial \beta_1^2} & \cdots & \frac{\partial^2 \ell}{\partial \beta_0 \partial \beta_p} \\ \vdots & \ddots & \ddots & \vdots \\ \frac{\partial^2 \ell}{\partial \beta_p \partial \beta_0} & \frac{\partial^2 \ell}{\partial \beta_p \partial \beta_1} & \cdots & \frac{\partial^2 \ell}{\partial \beta_p^2} \end{bmatrix}\end{aligned}$$

Exercise 3.38. Determine the Hessian for the `beetles` model.

Solution 3.32. In the `beetles` model, the Hessian is:

$$
\begin{aligned}
\ell''(\beta) &= \begin{bmatrix} \frac{\partial \ell'}{\partial \beta_0} & \frac{\partial \ell'}{\partial \beta_1} \end{bmatrix} \\
&= \begin{bmatrix} \frac{\partial^2 \ell}{\partial \beta_0^2} & \frac{\partial^2 \ell}{\partial \beta_0 \partial \beta_1} \\ \frac{\partial^2 \ell}{\partial \beta_1 \partial \beta_0} & \frac{\partial^2 \ell}{\partial \beta_1^2} \end{bmatrix} \\
&= \begin{bmatrix} -\sum_{i=1}^n \pi_i(1-\pi_i) & -\sum_{i=1}^n c_i \pi_i(1-\pi_i) \\ -\sum_{i=1}^n c_i \pi_i(1-\pi_i) & -\sum_{i=1}^n c_i^2 \pi_i(1-\pi_i) \end{bmatrix}
\end{aligned}
$$

Setting $\ell'(\tilde{\beta}; \tilde{y}) = 0$ gives us:

$$
\sum_{i=1}^n \{\tilde{x}_i(y_i - \text{expit}\{\tilde{x}_i'\beta\})\} = 0 \tag{3.33}
$$

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

Instead, we can use the Newton-Raphson method:

$$
\hat{\theta}^* \leftarrow \hat{\theta}^* - \left(\ell''\left(\tilde{y}; \hat{\theta}^*\right)\right)^{-1} \ell'\left(\tilde{y}; \hat{\theta}^*\right)
$$

We make an iterative series of guesses, and each guess helps us make the next guess better (i.e., higher log-likelihood). You can see some information about this process like so:

```
beetles_glm_ungrouped <-
  beetles_long |>
  glm(
    control = glm.control(trace = TRUE),
    formula = outcome ~ dose,
    family = "binomial"
  )
#> Deviance = 383.249 Iterations - 1
#> Deviance = 372.921 Iterations - 2
#> Deviance = 372.472 Iterations - 3
#> Deviance = 372.471 Iterations - 4
#> Deviance = 372.471 Iterations - 5
```

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 5 iterations to converge to a solution where the likelihood wasn't changing much anymore.

Table 3.12 and Table 3.13 show the fitted model and the covariance matrix of the estimates, respectively.

Table 3.12.: Fitted model for `beetles` data

```
beetles_glm_ungrouped |> summary()
#>
#> Call:
#> glm(formula = outcome ~ dose, family = "binomial", data = beetles_long,
#>     control = glm.control(trace = TRUE))
#>
#> Coefficients:
#>             Estimate Std. Error z value Pr(>|z|)
#> (Intercept)   -60.72       5.18   -11.7   <2e-16 ***
#> dose           34.27       2.91    11.8   <2e-16 ***
#> ---
#> Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
#>
#> (Dispersion parameter for binomial family taken to be 1)
#>
#>     Null deviance: 645.44  on 480  degrees of freedom
#> Residual deviance: 372.47  on 479  degrees of freedom
#> AIC: 376.5
#>
#> Number of Fisher Scoring iterations: 5
```

Table 3.13.: Parameter estimate covariance matrix for `beetles` data

```
beetles_glm_ungrouped |> vcov()
#>             (Intercept)      dose
#> (Intercept)     26.8393 -15.08189
#> dose           -15.0819   8.48041
```

3.10. Inference for logistic regression models

3.10.1. Inference for individual predictor coefficients

3.10.1.1. Wald tests and confidence intervals

(to be added)

3.10.2. Inference for odds ratios

Exercise 3.39. Given a maximum likelihood estimate $\hat{\beta}$ and a corresponding estimated covariance matrix $\hat{\Sigma} \stackrel{\text{def}}{=} \widehat{\text{Cov}}(\hat{\beta})$, calculate a 95% confidence interval for the odds ratio comparing covariate patterns $\tilde{x}$ and $\tilde{x}^*$, $\theta(\tilde{x}, \tilde{x}^*)$.

Solution 3.33.

By Theorem F.6, a 95% confidence interval for $\theta(\tilde{x}, \tilde{x}^*)$ can be constructed as:

$$\hat{\theta} \pm 1.96 * \widehat{\text{SE}}\left(\hat{\theta}\right) \tag{3.34}$$

However, $\widehat{\text{SE}}\left(\hat{\theta}\right)$ seems difficult to compute; doing so would require using the delta method[8].

Instead, using the invariance property of MLEs, we can first calculate a confidence interval for the logarithm of the odds ratio,

$$\log\{\theta(\tilde{x}, \tilde{x}^*)\} \in (L, R) \tag{3.35}$$

and then exponentiate the endpoints of that log-odds-scale confidence interval:

$$\theta(\tilde{x}, \tilde{x}^*) \in (e^L, e^R) \tag{3.36}$$

Exercise 3.40. Find a 95% confidence interval for the natural logarithm of the odds ratio, $\log\{\theta(\tilde{x}, \tilde{x}^*)\}$

---

[8] https://en.wikipedia.org/wiki/Delta_method

Solution 3.34. From Corollary 3.12, we know:

$$\log\{\theta(\tilde{x}, \tilde{x}^*)\} = \Delta\eta$$

By Theorem F.6, a 95% confidence interval for $\Delta\eta$ can be constructed as:

$$\widehat{\Delta\eta} \pm 1.96 * \widehat{\mathrm{SE}}\left(\widehat{\Delta\eta}\right)$$

Exercise 3.41.

How can we estimate the standard error of $\widehat{\Delta\eta}$?

$$\widehat{\mathrm{SE}}\left(\widehat{\Delta\eta}\right) = ?$$

Solution 3.35.

$$\mathrm{SE}\left(\widehat{\Delta\eta}\right) = \sqrt{\mathrm{Var}\left(\widehat{\Delta\eta}\right)} \tag{3.37}$$

By Lemma 3.8 and Theorem C.17:

$$\begin{aligned}
\mathrm{Var}\left(\widehat{\Delta\eta}\right) &= \mathrm{Var}\left((\Delta\tilde{x}) \cdot \hat{\beta}\right) \\
&= (\Delta\tilde{x})^\top \mathrm{Cov}\left(\hat{\beta}\right)(\Delta\tilde{x}) \\
&= (\Delta\tilde{x})^\top \Sigma(\Delta\tilde{x})
\end{aligned} \tag{3.38}$$

where $\Sigma \stackrel{\text{def}}{=} \mathrm{Cov}(\hat{\beta})$.

Expanding Equation 3.38 out of matrix-vector notation, we have:

$$\begin{aligned}
(\Delta\tilde{x})^\top \Sigma(\Delta\tilde{x}) &= \sum_{i=1}^{p}\sum_{j=1}^{p}(\Delta\tilde{x})_i \Sigma_{ij} (\Delta\tilde{x})_j \\
&= \sum_{i=1}^{p}\sum_{j=1}^{p}(\Delta x_i)\Sigma_{ij}(\Delta x_j) \\
&= \sum_{i=1}^{p}\sum_{j=1}^{p}(x_i - x_i^*)\mathrm{Cov}(\hat{\beta}_i, \hat{\beta}_j)(x_j - x_j^*)
\end{aligned}$$

Combining Equation 3.38 and MLE invariance:

Theorem 3.27 (Estimated variance and standard error of difference in log-odds).

$$\widehat{Var}(\Delta\hat{\eta}) = \Delta\tilde{x}^\top \hat{\Sigma}(\Delta\tilde{x}) \tag{3.39}$$

$$\widehat{SE}(\Delta\hat{\eta}) = \sqrt{\Delta\tilde{x}^\top \hat{\Sigma}(\Delta\tilde{x})} \tag{3.40}$$

Note: on the RHS, we have plugged in $\hat{\Sigma}$, our estimate of Σ.

Compare this result with Section 2.7.3.

3.11. Multiple logistic regression

3.11.1. 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)".

Exercise 3.42. What is "type A" behavior?

Solution 3.36. *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."

3.11.1.1. 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.

3.11.2. 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.

Table 3.14.: `wcgs` data

```
wcgs
#> # A tibble: 3,154 x 22
#>      age arcus behpat   bmi chd69  chol   dbp dibpat height    id lnsbp lnwght
#>    <dbl> <lgl> <fct>  <dbl> <fct> <dbl> <dbl> <fct>   <dbl> <dbl> <dbl>  <dbl>
#>  1    50 TRUE  A1      31.3 No      249    90 Type A     67  2343  4.88   5.30
#>  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      22.1 No      173    80 Type A     69 22057  4.84   5.01
#>  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
#>  7    40 FALSE A1      23.2 No      190    78 Type A     70  3894  4.80   5.09
#>  8    41 FALSE A1      23.0 No      212    84 Type A     70 11389  4.87   5.08
#>  9    50 TRUE  A1      27.2 No      130    70 Type A     71 12681  4.72   5.27
#> 10    43 FALSE A1      28.4 No      233    80 Type A     68 10005  4.79   5.23
#> # i 3,144 more rows
#> # i 10 more variables: ncigs <dbl>, sbp <dbl>, smoke <fct>, t1 <dbl>,
#> #   time169 <dbl>, typchd69 <fct>, uni <dbl>, weight <dbl>, wghtcat <fct>,
#> #   agec <fct>
```

Later surveys added data on:

- anthropometry
- triglycerides
- Jenkins Activity Survey
- caffeine use

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

3.11.3. 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)
```

3.11.4. Data cleaning

Now let's do some data cleaning

```r
library(arsenal) # provides `set_labels()`
library(forcats) # provides `as_factor()`
library(haven)
library(plotly)
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 B") |>
      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
    )
  )
```

3.11.5. What's in the data

Table 3.15 summarizes the data.

3.11.6. 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:

Table 3.15.: Baseline characteristics by CHD status at end of follow-up

```
library(gtsummary)
wcgs |>
  dplyr::select(
    -dplyr::all_of(c("id", "uni", "t1"))
  ) |>
  gtsummary::tbl_summary(
    by = "chd69",
    missing_text = "Missing"
  ) |>
  gtsummary::add_p() |>
  gtsummary::add_overall() |>
  gtsummary::bold_labels() |>
  gtsummary::separate_p_footnotes()
```

Characteristic	**Overall** N = 3,154[1]	**No** N = 2,897[1]	**Yes** N = 2
Age (years)	45.0 (42.0, 50.0)	45.0 (41.0, 50.0)	49.0 (44.0, 5
Arcus Senilis	941 (30%)	839 (29%)	102 (40%
Missing	2	0	2
Behavioral Pattern			
A1	264 (8.4%)	234 (8.1%)	30 (12%
A2	1,325 (42%)	1,177 (41%)	148 (58%
B3	1,216 (39%)	1,155 (40%)	61 (24%
B4	349 (11%)	331 (11%)	18 (7.0%
Body Mass Index (kg/m2)	24.39 (22.96, 25.84)	24.39 (22.89, 25.84)	24.82 (23.63,
Total Cholesterol	223 (197, 253)	221 (195, 250)	245 (222, 2
Missing	12	12	0
Diastolic Blood Pressure	80 (76, 86)	80 (76, 86)	84 (80, 9
Behavioral Pattern			
Type B	1,565 (50%)	1,486 (51%)	79 (31%
Type A	1,589 (50%)	1,411 (49%)	178 (69%
Height (inches)	70.00 (68.00, 72.00)	70.00 (68.00, 72.00)	70.00 (68.00,
Ln of Systolic Blood Pressure	4.84 (4.79, 4.91)	4.84 (4.77, 4.91)	4.87 (4.82, 4
Ln of Weight	5.14 (5.04, 5.20)	5.13 (5.04, 5.20)	5.16 (5.09, 5
Cigarettes per day	0 (0, 20)	0 (0, 20)	20 (0, 30
Systolic Blood Pressure	126 (120, 136)	126 (118, 136)	130 (124, 1
Current smoking	1,502 (48%)	1,343 (46%)	159 (62%
Observation (follow up) time (days)	2,942 (2,842, 3,037)	2,952 (2,864, 3,048)	1,666 (934, 2
Type of CHD Event			
None	0 (0%)	0 (0%)	0 (0%)
infdeath	2,897 (92%)	2,897 (100%)	0 (0%)
silent	135 (4.3%)	0 (0%)	135 (53%
angina	71 (2.3%)	0 (0%)	71 (28%
4	51 (1.6%)	0 (0%)	51 (20%
Weight (lbs)	170 (155, 182)	169 (155, 182)	175 (162, 1
Weight Category			
< 140	232 (7.4%)	217 (7.5%)	15 (5.8%
140-170	1,538 (49%)	1,440 (50%)	98 (38%
170-200	1,171 (37%)	1,049 (36%)	122 (47%
> 200	213 (6.8%)	191 (6.6%)	22 (8.6%
RECODE of age (Age)			
35-40	543 (17%)	512 (18%)	31 (12%

```r
library(dplyr)
odds <- function(pi) pi / (1 - pi)
chd_grouped_data <-
  wcgs |>
  summarize(
    .by = c(age, dibpat),
    n = sum(chd69 %in% c("Yes", "No")),
    x = sum(chd69 == "Yes")
  ) |>
  mutate(
    `n - x` = n - x,
    `p(chd)` = (x / n) |>
      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 8
#>      age dibpat     n     x `n - x` `p(chd)`  `odds(chd)` `logit(chd)`
#>    <dbl> <fct>  <int> <int>   <int> <dbl+lbl>       <dbl>        <dbl>
#>  1    50 Type A    76     8      68 0.105          0.118         -2.14
#>  2    51 Type A    67    11      56 0.164          0.196         -1.63
#>  3    59 Type A    30     7      23 0.233          0.304         -1.19
#>  4    44 Type A   113     9     104 0.0796         0.0865        -2.45
#>  5    47 Type A    72     7      65 0.0972         0.108         -2.23
#>  6    40 Type A   133     9     124 0.0677         0.0726        -2.62
#>  7    41 Type A   108     7     101 0.0648         0.0693        -2.67
#>  8    43 Type A    97     7      90 0.0722         0.0778        -2.55
#>  9    54 Type A    53     7      46 0.132          0.152         -1.88
#> 10    48 Type A    80    12      68 0.15           0.176         -1.73
#> # i 32 more rows
```

3.11.7. Graphical exploration

```r
library(ggplot2)
library(scales)
chd_plot_probs <-
  chd_grouped_data |>
  ggplot() +
  aes(
      x = age,
      y = `p(chd)`,
      col = dibpat
    ) +
  geom_point(aes(size = n), alpha = .7) +
  scale_size(range = c(1, 4)) +
  geom_line() +
  theme_bw() +
```

```
  ylab("P(CHD Event by 1969)") +
  scale_y_continuous(
    labels = scales::label_percent(),
    sec.axis = sec_axis(
      ~ odds(.),
      name = "odds(CHD Event by 1969)"
    )
  ) +
  theme(legend.position = "bottom")

print(chd_plot_probs)
```

Figure 3.12.: CHD rates by age group, probability scale

3.11.7.1. Odds scale

```
odds_inv <- function(omega) omega / (1 + omega)
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
```

```
    name = chd_plot_probs$labels$y,
    sec.axis = sec_axis(
      ~ odds(.),
      name = "odds(CHD Event by 1969)"
    )
  )

print(chd_plot_odds)
```

Figure 3.13.: CHD rates by age group, odds spacing

3.11.7.2. Log-odds (logit) scale

```
logit <- function(pi) log(odds(pi))
expit <- function(eta) odds_inv(exp(eta))
trans_logit <- trans_new(
  name = "logit",
  transform = logit,
  inverse = expit
)

chd_plot_logit <-
  chd_plot_probs +
  scale_y_continuous(
    trans = trans_logit, # this line changes the vertical spacing
    name = chd_plot_probs$labels$y,
```

```
    breaks = c(seq(.01, .1, by = .01), .15, .2),
    minor_breaks = NULL,
    sec.axis = sec_axis(
      ~ logit(.),
      name = "log(odds(CHD Event by 1969))"
    )
  )

print(chd_plot_logit)
```

Figure 3.14.: CHD data (logit-scale)

3.11.8. Logistic regression models for CHD data

For the `wgcs` dataset, let's consider a **logistic regression model** for the outcome of Coronary Heart Disease (Y; `chd` in computer output):

- $Y = 1$ if an individual developed CHD by the end of the study;
- $Y = 0$ if they have not developed CHD by the end of the study.

Let's include an intercept, two covariates, plus their interaction:

- A: age at study enrollment (`age`, recorded in years)
- P: personality type (`dibpat`):
  - $P = 1$ represents "Type A personality",
  - $P = 0$ represents "Type B personality".
- PA: the interaction of personality type and age (`dibpat:age`)
- $\tilde{X} = (1, A, P, PA)$

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

library(equatiomatic)
equatiomatic::extract_eq(chd_glm_contrasts)
```

$$\log\left[\frac{P(\text{chd69} = \text{Yes})}{1 - P(\text{chd69} = \text{Yes})}\right] = \alpha + \beta_1(\text{dibpat}_{\text{Type A}}) + \beta_2(\text{age}) + \beta_3(\text{dibpat}_{\text{Type A}} \times \text{age}) \tag{3.41}$$

Or in more formal notation:

$$\begin{aligned} Y_i|\tilde{X}_i &\sim_{\perp\!\!\!\perp} \text{Ber}(\pi(\tilde{X}_i)) \\ \pi(\tilde{x}) &= \text{expit}(\eta(\tilde{x})) \\ \eta(\tilde{x}) &= \beta_0 + \beta_P p + \beta_A a + \beta_{PA} pa \end{aligned} \tag{3.42}$$

3.11.9. Models superimposed on data

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

3.11.9.1. probability scale

```
curve_type_A <- function(x) { # nolint: object_name_linter
  chd_glm_contrasts |> predict(
    type = "response",
    newdata = tibble(age = x, dibpat = "Type A")
  )
}

curve_type_B <- function(x) { # nolint: object_name_linter
  chd_glm_contrasts |> 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)
```

```
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)
```

odds scale

3.11.9.2. log-odds (logit) scale

```
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)
```

Figure 3.15.

3.11.10. Interpreting the model parameters

Exercise 3.43. For Equation 3.42, derive interpretations of β_0, β_P, β_A, and β_{PA} on the odds **and** log-odds scales, State the interpretations concisely in math **and** in words.

Solution 3.37.

```
# include: false
age_offset = 0L
```

$$\begin{aligned}\eta(P=0, A=0) &= \beta_0 + \beta_P 0 + \beta_A 0 \\ &= \beta_0 + 0 + 0 \\ &= \beta_0\end{aligned}$$

Therefore:

$$\beta_0 = \eta(P=0, A=0) \tag{3.43}$$

β_0 is the natural logarithm of the odds ("log-odds") of experiencing CHD for a 0 year-old person with a type B personality; that is,

---

e^{β_0} is the odds of experiencing CHD for a 0 year-old with a type B personality,

$$\begin{aligned}\exp\{\beta_0\} &= \frac{\Pr(Y=1|P=0,A=0)}{1-\Pr(Y=1|P=0,A=0)} \\ &= \frac{\Pr(Y=1|P=0,A=0)}{\Pr(Y=0|P=0,A=0)}\end{aligned}$$

$$\begin{aligned}\frac{\partial}{\partial a}\eta(P=0,A=a) &= \frac{\partial}{\partial a}(\beta_0+\beta_P 0+\beta_A a+\beta_{PA}(0\cdot a)) \\ &= \frac{\partial}{\partial a}\beta_0+\frac{\partial}{\partial a}\beta_P 0+\frac{\partial}{\partial a}\beta_A a+\frac{\partial}{\partial a}\beta_{PA}(0\cdot a)) \\ &= 0+0+\beta_A+0 \\ &= \beta_A\end{aligned}$$

Therefore:

$$\beta_A = \frac{\partial}{\partial a}\eta(P=0,A=a) \tag{3.44}$$

β_A is the slope of the log-odds of CHD with respect to age, for individuals with personality type B.

Alternatively:

$$\beta_A = \eta(P=0,A=a+1)-\eta(P=0,A=a)$$

That is, β_A is the difference in log-odds of experiencing CHD experiencing CHD per one-year difference in age between two individuals with type B personalities.

$$\begin{aligned}\exp\{\beta_A\} &= \exp\{\eta(P=0,A=a+1)-\eta(P=0,A=a)\} \\ &= \frac{\exp\{\eta(P=0,A=a+1)\}}{\exp\{\eta(P=0,A=a)\}} \\ &= \frac{\omega(P=0,A=a+1)}{\omega(P=0,A=a)} \\ &= \frac{\text{odds}(Y=1|P=0,A=a+1)}{\text{odds}(Y=1|P=0,A=a)} \\ &= \theta(\Delta a=1|P=0)\end{aligned}$$

- The odds ratio of experiencing CHD (aka "the odds ratio") differs by a factor of e^{β_A} per one-year difference in age between individuals with type B personality.

β_P is the difference in log-odds of experiencing CHD for a 0 year-old person with type A personality compared to a 0 year-old person with type B personality; that is,

$$\beta_P = \eta(P = 1, A = 0) - \eta(P = 0, A = 0) \tag{3.45}$$

- e^{β_P} is the ratio of the odds (aka "the odds ratio") of experiencing CHD, for a 0-year old individual with type A personality vs a 0-year old individual with type B personality; that is,

$$\exp\{\beta_P\} = \frac{\text{odds}(Y = 1|P = 1, A = 0)}{\text{odds}(Y = 1|P = 0, A = 0)}$$

$$\frac{\partial}{\partial a}\eta(P = 1, A = a) = \beta_A + \beta_{PA}$$
$$\frac{\partial}{\partial a}\eta(P = 0, A = a) = \beta_A$$

Therefore:

$$\begin{aligned}\frac{\partial}{\partial a}\eta(P = 1, A = a) - \frac{\partial}{\partial a}\eta(P = 0, A = a) &= \beta_A + \beta_{PA} - \beta_A \\ &= \beta_{PA}\end{aligned}$$

That is,

$$\begin{aligned}\beta_{PA} &= \frac{\partial}{\partial a}\eta(P = 1, A = a) - \frac{\partial}{\partial a}\eta(P = 0, A = a) \\ &= \frac{\partial}{\partial a}\eta(P = 1, A = a) - \frac{\partial}{\partial a}\eta(P = 0, A = a)\end{aligned}$$

β_{PA} is the difference in the slopes of log-odds over age between participants with Type A personalities and participants with Type B personalities.

Accordingly, the odds ratio of experiencing CHD per one-year difference in age differs by a factor of $e^{\beta_{PA}}$ for participants with type A personality compared to participants with type B personality; that is,

$$\theta(\Delta a = 1|P = 1) = \exp\{\beta_{PA}\} \times \theta(\Delta a = 1|P = 0)$$

or equivalently:

$$\exp\{\beta_{PA}\} = \frac{\theta(\Delta a = 1|P = 1)}{\theta(\Delta a = 1|P = 0)}$$

See Section 5.1.1[9] of Vittinghoff et al. (2012) for another perspective, also using the `wcgs` data as an example.

3.11.11. Interpreting the model parameter estimates

Table 3.16 shows the fitted model.

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

Table 3.16.: CHD model (corner-point parametrization)

Parameter	Log-Odds	SE	95% CI	z	p
(Intercept)	-5.80	0.98	(-7.73, -3.90)	-5.95	< .001
dibpat (Type A)	0.30	1.18	(-2.02, 2.63)	0.26	0.797
age	0.06	0.02	(0.02, 0.10)	3.01	0.003
dibpat (Type A) × age	0.01	0.02	(-0.04, 0.06)	0.42	0.674

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

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

Table 3.17.: Odds ratio estimates for CHD model

Parameter	Odds Ratio	SE	95% CI	z	p
(Intercept)	3.02e-03	2.94e-03	(4.40e-04, 0.02)	-5.95	< .001
dibpat (Type A)	1.36	1.61	(0.13, 13.88)	0.26	0.797
age	1.06	0.02	(1.02, 1.11)	3.01	0.003
dibpat (Type A) × age	1.01	0.02	(0.96, 1.06)	0.42	0.674

3.11.12. Stratified parametrization

We could instead use a stratified parametrization:

[9] https://link.springer.com/chapter/10.1007/978-1-4614-1353-0_5#Sec2_5

```
chd_glm_strat <- glm(
  "formula" = chd69 == "Yes" ~ dibpat + dibpat:age - 1,
  "data" = wcgs,
  "family" = binomial(link = "logit")
)
equatiomatic::extract_eq(chd_glm_strat)
```

$$\log\left[\frac{P(\text{chd69} = \text{Yes})}{1 - P(\text{chd69} = \text{Yes})}\right] = \beta_1(\text{dibpat}_{\text{Type B}}) + \beta_2(\text{dibpat}_{\text{Type A}}) + \beta_3(\text{dibpat}_{\text{Type B}} \times \text{dibpat}_{\text{age}}) + \beta_4(\text{dibpat}_{\text{Type} \tag{3.46}}$$

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

Table 3.18.: CHD model, stratified parametrization

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

Again, we can get the corresponding odds ratios (e^{β}s) by passing `exponentiate = TRUE` to `parameters()`:

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

Table 3.19.: Odds ratio estimates for CHD model

Parameter	Odds Ratio	SE	95% CI	z	p
dibpat (Type B)	3.02e-03	2.94e-03	(4.40e-04, 0.02)	-5.95	< .001
dibpat (Type A)	4.09e-03	2.75e-03	(1.08e-03, 0.02)	-8.18	< .001
dibpat (Type B) × age	1.06	0.02	(1.02, 1.11)	3.01	0.003
dibpat (Type A) × age	1.07	0.01	(1.05, 1.10)	5.24	< .001

Compare with Table 3.16.

Exercise 3.44. If I give you model 1, how would you get the coefficients of model 2?

3.12. Model comparisons for logistic models

3.12.1. 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.

> 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.

3.12.2. 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_contrasts |> fitted(),
    pred_prob_cats1 = pred_probs_glm1 |>
      cut(
        breaks = seq(0, 1, by = .1),
        include.lowest = TRUE
      )
```

```
  )

HL_table <- # nolint: object_name_linter
  wcgs |>
  summarize(
    .by = pred_prob_cats1,
    n = n(),
    o = sum(chd69 == "Yes"),
    e = sum(pred_probs_glm1)
  )

library(pander)
HL_table |> pander()
```

pred_prob_cats1	n	o	e
(0.1,0.2]	785	116	108
(0.2,0.3]	64	12	13.77
[0,0.1]	2,305	129	135.2

```
X2 <- HL_table |> # nolint: object_name_linter
  summarize(
    `X^2` = sum((o - e)^2 / e)
  ) |>
  pull(`X^2`)
print(X2)
#> [1] 1.11029

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

Our statistic is $X^2 = 1.110287$; $p(\chi^2(1) > 1.110287) = 0.29202$, 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_contrasts |> fitted(),
    pred_prob_cats1 = pred_probs_glm1 |>
      cut(
        breaks = quantile(pred_probs_glm1, seq(0, 1, by = .1)),
        include.lowest = TRUE
      )
  )

HL_table <- # nolint: object_name_linter
```

```
  wcgs |>
  summarize(
    .by = pred_prob_cats1,
    n = n(),
    o = sum(chd69 == "Yes"),
    e = sum(pred_probs_glm1)
  )

HL_table |> pander()
```

pred_prob_cats1	n	o	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

```
X2 <- HL_table |> # nolint: object_name_linter
  summarize(
    `X^2` = sum((o - e)^2 / e)
  ) |>
  pull(`X^2`)

print(X2)
#> [1] 6.78114

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

Now we have more evenly split categories. The p-value is 0.56042, still not significant.

Graphically, we have compared:

```
HL_plot <- # nolint: object_name_linter
  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)
```

3.12.3. 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]

3.13. Residual-based diagnostics

3.13.1. Logistic regression residuals only work for grouped data

```
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"
)
library(here) # provides the `here()` function
library(fs) # provides the `path()` function
here::here() |>
  fs::path("Data/wcgs.rda") |>
  load()
chd_glm_contrasts <-
```

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

Figure 3.16.: Residual diagnostics for WCGS model with individual-level observations

---

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:

```
library(dplyr)
wcgs_grouped <-
  wcgs |>
  summarize(
    .by = c(dibpat, age),
    n = n(),
    chd = sum(chd69 == "Yes"),
    no_chd = sum(chd69 == "No")
  ) |>
  mutate(p_chd = chd/n)

chd_glm_contrasts_grouped <- glm(
  "formula" = cbind(chd, no_chd) ~ dibpat*age,
```

```
  "data" = wcgs_grouped,
  "family" = binomial(link = "logit")
)
chd_glm_contrasts_grouped |> equatiomatic::extract_eq()
```

$$\log\left[\frac{P(\text{chd})}{1-P(\text{chd})}\right] = \alpha + \beta_1(\text{dibpat}_{\text{Type A}}) + \beta_2(\text{age}) + \beta_3(\text{dibpat}_{\text{Type A}} \times \text{age}) \tag{3.47}$$

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

Table 3.22.: CHD model with grouped `wcgs` data

Parameter	Log-Odds	SE	95% CI	z	p
(Intercept)	-5.80	0.98	(-7.73, -3.90)	-5.95	< .001
dibpat (Type A)	0.30	1.18	(-2.02, 2.63)	0.26	0.797
age	0.06	0.02	(0.02, 0.10)	3.01	0.003
dibpat (Type A) × age	0.01	0.02	(-0.04, 0.06)	0.42	0.674

```
chd_glm_contrasts_grouped |>
  sjPlot::plot_model(type = "pred", terms = c("age", "dibpat")) +
  geom_point(data = wcgs_grouped |> mutate(group_col = dibpat),
             aes(x = age, y = p_chd))
```

Figure 3.17.: CHD model with grouped `wcgs` data

```
library(ggfortify)
chd_glm_contrasts_grouped |> autoplot()
```

3.13.2. (Response) residuals

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

(k indexes the covariate patterns)

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

```
odds <- function(pi) pi/(1-pi)
logit <- function(pi) log(odds(pi))
wcgs_grouped <-
  wcgs_grouped |>
  mutate(
    fitted = chd_glm_contrasts_grouped |> fitted(),
    fitted_logit = fitted |> logit(),
    response_resids = chd_glm_contrasts_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::loess`; `stats::lowess` is older, hard to use with `geom_smooth`, and hard to match exactly with `stats::loess`; see https://support.bioconductor.org/p/2323/.]

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

Figure 3.18.: residuals plot for `wcgs` model

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 $\pi = 0.5$).

3.13.3. 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

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

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_contrasts_grouped, which = 1, ncol = 1) |> print()
```

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

3.13.3.1. 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:

```
library(glmx)
library(dplyr)
data(BeetleMortality)
beetles <- BeetleMortality |>
  mutate(
    pct = died / n,
    survived = n - died,
    dose_c = dose - mean(dose)
  )
beetles_glm_grouped <- beetles |>
  glm(
    formula = cbind(died, survived) ~ dose,
    family = "binomial"
  )
autoplot(beetles_glm_grouped, which = 1, ncol = 1) |> print()
```

3.13.3.2. Pearson residuals with individual (ungrouped) data

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

```
library(ggfortify)
```

```
chd_glm_strat <- glm(
  "formula" = chd69 == "Yes" ~ dibpat + dibpat:age - 1,
  "data" = wcgs,
  "family" = binomial(link = "logit")
)

autoplot(chd_glm_strat, which = 1, ncol = 1) |> print()
```

Meaningless.

3.13.3.3. 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_contrasts_grouped |> fitted(),
    fitted_logit = fitted |> logit(),
    resids = chd_glm_contrasts_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"
    ),
    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/
```

```
wcgs_resid_plot1 |> print()
```

3.13.4. 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), $X^2 \dot{\sim} \chi^2(N-p)$.

```
x_pearson <- chd_glm_contrasts_grouped |>
  resid(type = "pearson")

chisq_stat <- sum(x_pearson^2)

pval <- pchisq(
  chisq_stat,
```

```
  lower = FALSE,
  df = length(x_pearson) - length(coef(chd_glm_contrasts_grouped))
)
```

For our CHD model, the p-value for this test is 0.265236; no significant evidence of a lack of fit at the 0.05 level.

3.13.4.1. 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.

3.13.5. 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).

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

3.13.5.1. Standardized deviance residuals

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

3.13.6. Diagnostic plots

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

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

Figure 3.19.: Diagnostics for CHD model

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

3.13.6.1. Beetles

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

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

Figure 3.20.: Diagnostics for logistic model of `BeetleMortality` data

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

3.14. Alternatives to reporting odds ratios

3.14.1. Objections to odds ratios

Some scholars have raised objections to the use of odds ratios as an effect measurement (Sackett, Deeks, and Altman 1996; Norton et al. 2024).

As we saw in Figure 3.3, the odds ratio is not very closely correlated with the risk difference, and the risk difference is typically the metric that ultimately matters for policy decisions.

Another objection is that odds ratios (and risk ratios, and risk differences) depend on the set of covariates in a logistic regression model, even when those covariates are independent of the exposure of interest and do not interact with that exposure. For example, consider the following model:

$$\mathrm{P}(Y = y|X = x, C = c) = \pi(x, c)^y (1 - \pi(x, c))^{1-y}$$

$$\pi(x, c) = \mathrm{expit}\{\eta_0 + \beta_X x + \beta_C c\}$$

Then:

$$\begin{aligned}
\mathrm{E}[Y|X = x] &= \mathrm{E}[\mathrm{E}[Y|X, C]|X = x] \\
&= \mathrm{E}[\pi(X, C)|X = x] \\
&= \mathrm{E}[\mathrm{expit}\{\eta_0 + \beta_X X + \beta_C C\}|X = x] \\
&= \int_c \mathrm{expit}\{\eta_0 + \beta_X x + \beta_C c\}\ \mathrm{p}(C = c|X = x)\ \partial c \\
&= \int_c \pi(x, c)\ \mathrm{p}(C = c|X = x)\ \partial c
\end{aligned}$$

Since the expit{} function is nonlinear, we can't change the order of the expectation and expit{} operators:

$$\mathrm{E}[\mathrm{expit}\{\eta_0 + \beta_X X + \beta_C C\}|X] \neq \mathrm{expit}\{\mathrm{E}[\eta_0 + \beta_X X + \beta_C C]|X\}$$

In contrast, consider a model with an identity link function:

$$\mathrm{P}(Y = y|X = x, C = c) = \pi(x, c)^y (1 - \pi(x, c))^{1-y}$$

$$\pi(x, c) = \eta_0 + \beta_X x + \beta_C c$$

Then:

$$\begin{aligned}
\mathrm{E}[Y|X = x] &= \mathrm{E}[\mathrm{E}[Y|X, C]|X = x] \\
&= \mathrm{E}[\eta_0 + \beta_X X + \beta_C C|X = x] \\
&= \mathrm{E}[\eta_0|X = x] + \mathrm{E}[\beta_X X|X = x] + \mathrm{E}[\beta_C C|X = x] \\
&= \eta_0 + \beta_X x + \beta_C \mathrm{E}[C|X = x] \\
&= (\eta_0 + \beta_C \mathrm{E}[C|X = x]) + \beta_X x
\end{aligned}$$

If $C \perp\!\!\!\perp X$, then $\mathrm{E}[C|X = x] = \mathrm{E}[C]$, and we can simplify further:

$$\begin{aligned}
\mathrm{E}[Y|X = x] &= (\eta_0 + \beta_C \mathrm{E}[C|X = x]) + \beta_X x \\
&= (\eta_0 + \beta_C \mathrm{E}[C]) + \beta_X x \\
&= \eta_0^* + \beta_X x
\end{aligned}$$

Then:

$$\frac{\partial}{\partial x}\mathrm{E}[Y|X=x] = \beta_X = \frac{\partial}{\partial x}\mathrm{E}[Y|X=x, C=c]$$

In other words, for a model with an identity link function, if covariates X and C are independent, then the slope with respect to X doesn't depend on whether C is included in the model (and an analogous result holds if X is discrete or categorical).

Exercise 3.45. What are the expressions for $\mathrm{E}[Y|X=x]$ and $\frac{\partial}{\partial x}\mathrm{E}[Y|X=x]$ for the model above, if $\mathrm{E}[C|X=x] = \gamma_0 + \gamma_x x$?

Solution 3.38. Left to the reader.

Exercise 3.46. What are the expressions for $\mathrm{E}[Y|X=x]$ and $\frac{\partial}{\partial x}\mathrm{E}[Y|X=x]$, if instead of the model above,

$$\pi(x,c) = \eta_0 + \beta_X x + \beta_C c + \beta_{XC} xc$$

and $\mathrm{E}[C|X=x] = \gamma_0 + \gamma_x x$?

Solution 3.39. Left to the reader.

Hint: does adding the interaction term change the functional form of $\mathrm{E}[Y|X=x]$?

3.14.2. Deriving risk ratios and risk differences from logistic regression models

If you want to report risk differences or risk ratios instead of odds ratios, you can obtain estimates from logistic regression models, as long as you didn't stratify sampling by the outcome; in other words, not in case-control studies (see Section 3.4.3.4).

To compute risk ratios from logistic regression models:

- Apply the expit function to the linear predictor for each covariate pattern to compute the (estimated) risks,
- Then take the differences or ratios of the risks, as needed.

To quantify uncertainty for risk difference or risk ratio estimates derived from logistic regression models (e.g., to calculate SEs, CIs, and p-values), you will need to use the bootstrap, the multivariate delta method, or some other special technique.

3.14.3. Other link functions for Bernoulli outcomes

Alternatively, if you want to estimate risk ratios more directly from the model, you can sometimes change the link function from logit{} to log{}; then you can obtain risk ratios by exponentiating coefficients [10], just like we did for odds ratios with the logit link:

```
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	p
(Intercept)	-0.80	0.12	(-1.04, -0.58)	-6.81	< .001
storage	0.17	0.07	(0.02, 0.31)	2.31	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:

[10] or linear combinations of coefficients, depending on what covariate patterns you are contrasting

```
anthers_glm_logit <- glm(
  formula = cbind(y, n - y) ~ storage,
  data = anthers_sum,
  family = binomial(link = "logit")
)

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

Parameter	Odds Ratio	SE	95% CI	z	p
(Intercept)	0.76	0.20	(0.45, 1.27)	-1.05	0.296
storage	1.49	0.26	(1.06, 2.10)	2.29	0.022

[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.

3.14.4. WCGS: link functions

```
wcgs_glm_logit_link <- chd_grouped_data |>
  mutate(type = relevel(dibpat, ref = "Type B")) |>
  glm(
    "formula" = cbind(x, `n - x`) ~ dibpat * age,
    "data" = _,
    "family" = binomial(link = "logit")
  )

wcgs_glm_identity_link <-
  chd_grouped_data |>
  mutate(type = relevel(dibpat, ref = "Type B")) |>
  glm(
    "formula" = cbind(x, `n - x`) ~ dibpat * age,
    "data" = _,
    "family" = binomial(link = "identity")
  )
wcgs_glm_identity_link |>
  coef() |>
  pander()
```

(Intercept)	dibpatType A	age	dibpatType A:age
-0.08257	-0.1374	0.002906	0.004194

```
library(ggfortify)
wcgs_glm_logit_link |> autoplot(which = c(1), ncol = 1) + facet_wrap(~dibpat)
wcgs_glm_identity_link |> autoplot(which = c(1), ncol = 1) + facet_wrap(~dibpat)
```

(a) Logistic link (b) Identity link

Figure 3.21.: Residuals vs Fitted plot for `wcgs` models

```
beetles_lm <-
  beetles_long |>
  lm(formula = died ~ dose)

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


beetles <-
  beetles |> mutate(
    resid_logit = beetles_glm_grouped |> resid(type = "response")
  )
beetles_glm_grouped |> autoplot(which = c(1), ncol = 1)
beetles_lm |> autoplot(which = c(1), ncol = 1)
```

(a) Logistic link (b) Identity link

Figure 3.22.: Residuals vs Fitted plot for `BeetleMortality` models

3.14.5. Quasibinomial

See Hua Zhou[11]'s lecture notes[12]

3.15. Further reading

- Hosmer, Lemeshow, and Sturdivant (2013) is a classic textbook on logistic regression

[11] https://hua-zhou.github.io/

[12] https://ucla-biostat-200c-2020spring.github.io/slides/04-binomial/binomial.html#:~:text=0.05%20%27.%27%200.1%20%27%20%27%201-,Quasi%2Dbinomial,-Another%20way%20to

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:

```
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(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' = 6)

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 default
legend_text_size = 9
run_graphs = TRUE
```

4.1. Introduction

This chapter presents models for count data outcomes. With covariates, the event rate λ becomes a function of the covariates $\tilde{X} = (X_1, \dots, X_n)$. Typically, count data models use a log{} link function, and thus an exp{} inverse-link function. That is:

$$\begin{aligned} \mathrm{E}[Y|\tilde{X} = \tilde{x}, T = t] &= \mu(\tilde{x}, t) \\ \mu(\tilde{x}, t) &= \lambda(\tilde{x}) \cdot t \\ \lambda(\tilde{x}) &= \exp\{\eta(\tilde{x})\} \\ \eta(\tilde{x}) &= \tilde{x}'\tilde{\beta} = \beta_0 + \beta_1 x_1 + \cdots + \beta_p x_p \end{aligned} \tag{4.1}$$

$T = t$ is called the *exposure magnitude* (Definition C.4) and has a special role in this model.

Exercise 4.1. Where have we seen a relationship like

$$\mu = \lambda \cdot t$$

before?

Solution 4.1. The relationship

$$\mu = \lambda \cdot t$$

in count regression models is analogous to the relationship

$$\mu = n\pi$$

in Binomial models.

We can also think of t as a special part of the linear component:

$$\begin{aligned}
\log\Big\{\mathrm{E}[Y|\tilde{X} = \tilde{x}, T = t]\Big\} &= \log\{\mu(\tilde{x})\} \\
&= \log\{\lambda(\tilde{x}) \cdot t\} \\
&= \log\{\lambda(\tilde{x})\} + \log t \\
&= \log\{\exp\{\eta(\tilde{x})\}\} + \log t \\
&= \eta(\tilde{x}) + \log t \\
&= \tilde{x}'\tilde{\beta} + \log t \\
&= (\beta_0 + \beta_1 x_1 + \cdots + \beta_p x_p) + \log t
\end{aligned}$$

In contrast with the other covariates (represented by $\tilde{X}$), t enters this expression with a log transformation and without a corresponding β coefficient; in other words, $\log\{t\}$ is an **offset term** (Definition C.8).

Exercise 4.2. What are the units of μ in Equation 4.1?

Solution 4.2. μ is the mean of Y, and Y is a count, so μ is also a count; for example:

- 3.1 cyclones,
- 10.23 ER visits
- 15.01 infections

Exercise 4.3. What are the units of λ in Equation 4.1?

Solution 4.3. $\lambda = \mu/t$, so λ is a rate of counts per unit of t. For example:

- 3.1 cyclones *per year*
- 2.023 ER visits per 10 person-years
- 15.01 infections per 1000 person-years at risk

4.2. Interpreting Poisson regression models

Differences on the log-rate scale become ratios on the rate scale, because

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

(recall from Algebra 2)

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

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

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

And accordingly,

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

4.3. Example: needle-sharing

(adapted from Vittinghoff et al. (2012), §8)

```r
library(tidyverse)
library(haven)
needles =
  "inst/extdata/needle_sharing.dta" |>
  read_dta() |>
  as_tibble() |>
  mutate(
    hivstat =
      hivstat |>
      case_match(
        1 ~ "HIV+",
        0 ~ "HIV-") |>
      factor() |>
      relevel(ref = "HIV-"),
    polydrug =
      polydrug |>
      case_match(
        1 ~ "multiple drugs used",
        0 ~ "one drug used") |>
      factor() |>
      relevel(ref = "one drug used"),
    homeless =
      homeless |>
      case_match(
        1 ~ "homeless",
        0 ~ "not homeless") |>
      factor() |>
      relevel(ref = "not homeless"),
    ethn = ethn |> factor() |> relevel(ref = "White"),
    sex = sex |> factor() |> relevel(ref = "M")
  ) |>
  labelled::set_variable_labels(
    "sex" = "sex (reference = Male)",
    "ethn" = "ethnicity (reference = White)",
    "shsyryn"  = "shared syringe yes/no (1 = yes, 0 = no)",
    "logshsyr" = "log(No. of shared needles)",
    "polydrug" = "how many drugs used?",
    "sqrtninj" = "sqrt(No. of infections in 30 days)",
    "homeless" = "Homeless (1 = yes, 0 = no)",
    "hivstat" = "HIV status (reference = HIV-)"
  )
```

```r
dict <- tibble(
  variable = names(needles),
  description = labelled::get_variable_labels(needles) |>
    sapply(function(x) ifelse(is.null(x), "", x)),
)
dict |> pander::pander()
```

Table 4.2.: Needle-sharing data

```
needles
#> # A tibble: 128 x 17
#>       id sex   ethn       age dprsn_dx sexabuse shared_syr hivstat hplsns nivdu
#>    <dbl> <fct> <fct>    <dbl>    <dbl>    <dbl>      <dbl> <fct>    <dbl> <dbl>
#>  1  2104 M     White       47        5        0          1 HIV-         6    90
#>  2  2009 M     White       39        1        0          1 HIV+         2     4
#>  3  2032 M     White       52        1        0          1 HIV-        18    90
#>  4  2063 M     AA          47        1        1          1 HIV-         1   120
#>  5  2059 M     Hispanic    32        1        0          2 HIV-        12   120
#>  6  2077 M     Hispanic    54        1        0          2 HIV-        10   120
#>  7  2042 F     White       32        5        0          2 HIV-         8    15
#>  8  2017 M     White       26        5        0          2 HIV-        11   120
#>  9  2119 M     White       54        1        0          3 HIV-         2    90
#> 10  2085 F     White       19        5        0          3 HIV-         7    90
#> # i 118 more rows
#> # i 7 more variables: shsyryn <dbl>, sqrtnivd <dbl>, logshsyr <dbl>,
#> #   polydrug <fct>, sqrtninj <dbl>, homeless <fct>, shsyr <dbl>
```

Table 4.1.: Data dictionary for `needles` data

variable	description
id	ID
sex	sex (reference = Male)
ethn	ethnicity (reference = White)
age	Age at 1st interview
dprsn_dx	DPRSN_DX
sexabuse	Sexually abused?
shared_syr	Shared syringe
hivstat	HIV status (reference = HIV-)
hplsns	HPLSNS
nivdu	No of injections (in 30 days)
shsyryn	shared syringe yes/no (1 = yes, 0 = no)
sqrtnivd	sqrt(No ivdu 30 days)
logshsyr	log(No. of shared needles)
polydrug	how many drugs used?
sqrtninj	sqrt(No. of infections in 30 days)
homeless	Homeless (1 = yes, 0 = no)
shsyr	No. of shared needles

```
library(ggplot2)

needles |>
  ggplot(
    aes(
      x = age,
      y = shsyryn,
      shape = sex,
      col = ethn
    )
  ) +
  geom_point(
    aes(size = nivdu),
    alpha = .5) +
  scale_size_area(max_size = 4) +
  facet_grid(
    cols = vars(polydrug),
    rows = vars(homeless)) +
  theme(legend.position = "bottom")
```

Figure 4.1.: Rates of needle sharing

4.3.0.1. Covariate counts

Table 4.3.: Counts of observations in `needles` dataset by sex, unhoused status, and multiple drug use

```
needles |>
  dplyr::select(sex, homeless, polydrug) |>
  summary()
#>     sex             homeless                 polydrug
#>  M    :97   not homeless:63   one drug used      :109
#>  F    :30   homeless    :61   multiple drugs used: 19
#>  Trans: 1   NA's        : 4
```

There's only one individual with `sex = Trans`, which unfortunately isn't enough data to analyze. We will remove that individual:

```
needles = needles |> filter(sex != "Trans")
```

4.3.1. Model

```
glm1 =
  needles |>
  dplyr::filter(nivdu > 0) |>
  glm(
    offset = log(nivdu),
    family = stats::poisson,
    formula = shared_syr ~ age + sex + homeless*polydrug
  )
library(equatiomatic)
equatiomatic::extract_eq(glm1)
```

$$\log(E(\text{shared}_{\text{s}}\text{yr})) = \alpha + \beta_1(\text{age}) + \beta_2(\text{sex}_{\text{F}}) + \beta_3(\text{homeless}) + \beta_4(\text{polydrug}) + \beta_5(\text{homeless} \times \text{polydrug}) + (\text{offset}) \tag{4.2}$$

```
library(parameters)
glm1 |> parameters(exponentiate = TRUE) |>
  print_md()
```

Table 4.4.: Poisson model for needle-sharing data

Parameter	IRR	SE	95% CI	z	p
(Intercept)	0.02	4.02e-03	(9.09e-03, 0.03)	-15.87	< .001
age	1.00	5.85e-03	(0.99, 1.01)	0.42	0.673
sex (F)	1.37	0.16	(1.09, 1.72)	2.73	0.006
homeless (homeless)	2.77	0.34	(2.18, 3.53)	8.30	< .001
polydrug (multiple drugs used)	2.85e-07	8.71e-05	(1.59e-267, 5.11e+253)	-0.05	0.961
homeless (homeless) × polydrug (multiple drugs used)	6.21e+05	1.90e+08	(3.47e-255, 1.11e+266)	0.04	0.965

```
library(sjPlot)
glm1 |>
  sjPlot::plot_model(
    type = "pred",
    terms = c("age", "sex", "homeless", "polydrug"),
    show.data = TRUE
  ) +
  theme(legend.position = "bottom")
```

Figure 4.2.

4.4. Inference for count regression models

4.4.1. Confidence intervals for regression coefficients and rate ratios

As usual:

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

Rate ratios: exponentiate CI endpoints

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

4.4.2. Hypothesis tests for regression coefficients

$$z = \frac{\hat{\beta} - \beta_0}{\widehat{\mathrm{se}}\left(\hat{\beta}\right)}$$

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

4.4.3. Comparing nested models

log(likelihood ratio) tests, as usual.

4.5. Prediction

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

4.6. Diagnostics

4.6.1. Residuals

4.6.1.1. Observation residuals

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

4.6.1.2. Pearson residuals

$$r = \frac{e}{\widehat{\mathrm{se}}(e)} \approx \frac{e}{\sqrt{\hat{y}}}$$

Table 4.5.: Diagnostics for Poisson model

4.6.1.3. Standardized Pearson residuals

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

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

4.6.1.4. Deviance residuals

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

> **Note**
>
> $$\text{sign}(x) \stackrel{\text{def}}{=} \frac{x}{|x|}$$
>
> In other words:
>
> - $\text{sign}(x) = -1$ if $x < 0$
> - $\text{sign}(x) = 0$ if $x = 0$
> - $\text{sign}(x) = 1$ if $x > 0$

```
library(ggfortify)
autoplot(glm1)
```

4.7. Zero-inflation

4.7.1. Models for zero-inflated counts

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

$$P(Z = 1|X = x) = \pi(x) = \text{expit}(\gamma_0 + \gamma_1 x_1 + ...)$$

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

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

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

Even though we never observe Z, we can estimate the parameters γ_0-γ_p, via maximum likelihood:

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

(by the Law of Total Probability)

where

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

Exercise 4.4. Expand $P(Y = 0|X = x, T = t)$, $P(Y = 1|X = x, T = t)$ and $P(Y = y|X = x, T = t)$ into expressions involving $P(Z = 1|X = x, T = t)$ and $P(Y = y|Z = 0, X = x, T = t)$.

Exercise 4.5. Derive the expected value and variance of Y, conditional on X and T, as functions of $P(Z = 1|X = x, T = t)$ and $\text{E}[Y|Z = 0, X = x, T = t]$.

4.8. Over-dispersion

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).

Definition 4.1 (Overdispersion)**.** A random variable X is **overdispersed** relative to a model $\text{p}(X = x)$ if if its empirical variance in a dataset is larger than the value is predicted by the fitted model $\hat{\text{p}}(X = x)$.

c.f. Dobson and Barnett (2018) §3.2.1, 7.7, 9.8; Vittinghoff et al. (2012) §8.1.5; and https://en.wikipedia.org/wiki/Overdispersion.

When we encounter overdispersion, we can try to reduce the residual variance by adding more covariates.

> **Note**
>
> Logistic regression is named after the (inverse) link function. Poisson regression is named after the outcome distribution. I think this naming convention reflects the strongest (most questionable assumption) in the model. In binary data regression, the outcome distribution essentially *must* be Bernoulli (or Binomial), but the link function could be logit, log, identity, probit, or something more unusual. In count data regression, the outcome distribution could have many different shapes, but the link function will probably end up being log, so that covariates have multiplicative effects on the rate.

4.8.1. Negative binomial models

There are alternatives to the Poisson model. Most notably, the negative binomial model.

We can still model μ as a function of X and T as before, and we can combine this model with zero-inflation (as the conditional distribution for the non-zero component).

4.8.1.1. Example: needle-sharing

```
library(MASS) #need this for glm.nb()
glm1.nb = glm.nb(
  data = needles,
  shared_syr ~ age + sex + homeless*polydrug
)

equatiomatic::extract_eq(glm1.nb)
```

$$\log(E(\text{shared}_{\text{s}}\text{yr})) = \alpha + \beta_1(\text{age}) + \beta_2(\text{sex}_{\text{F}}) + \beta_3(\text{homeless}) + \beta_4(\text{polydrug}) + \beta_5(\text{homeless} \times \text{polydrug}) \tag{4.3}$$

Table 4.6.: Negative binomial model for needle-sharing data

```
summary(glm1.nb)
#>
#> Call:
#> glm.nb(formula = shared_syr ~ age + sex + homeless * polydrug,
#>     data = needles, init.theta = 0.08436295825, link = log)
#>
#> Coefficients:
#>                                              Estimate Std. Error z value
#> (Intercept)                                  9.91e-01   1.71e+00    0.58
#> age                                         -2.76e-02   3.82e-02   -0.72
#> sexF                                         1.06e+00   8.07e-01    1.32
#> homelesshomeless                             1.65e+00   7.22e-01    2.29
#> polydrugmultiple drugs used                 -2.46e+01   3.61e+04    0.00
#> homelesshomeless:polydrugmultiple drugs used  2.32e+01   3.61e+04    0.00
#>                                             Pr(>|z|)
#> (Intercept)                                    0.563
#> age                                            0.469
#> sexF                                           0.187
#> homelesshomeless                               0.022 *
#> polydrugmultiple drugs used                    0.999
#> homelesshomeless:polydrugmultiple drugs used   0.999
#> ---
#> Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
#>
#> (Dispersion parameter for Negative Binomial(0.0844) family taken to be 1)
#>
#>     Null deviance: 69.193  on 119  degrees of freedom
#> Residual deviance: 57.782  on 114  degrees of freedom
#>   (7 observations deleted due to missingness)
#> AIC: 315.5
#>
#> Number of Fisher Scoring iterations: 1
#>
#>
#>               Theta:  0.0844
#>           Std. Err.:  0.0197
#>
#>  2 x log-likelihood:  -301.5060
```

Table 4.7.: Poisson versus Negative Binomial Regression coefficient estimates

```
tibble(name = names(coef(glm1)), poisson = coef(glm1), nb = coef(glm1.nb))
#> # A tibble: 6 x 3
#>   name                                          poisson       nb
#>   <chr>                                           <dbl>    <dbl>
#> 1 (Intercept)                                   -4.18      0.991
#> 2 age                                            0.00247  -0.0276
#> 3 sexF                                           0.316     1.06
#> 4 homelesshomeless                               1.02      1.65
#> 5 polydrugmultiple drugs used                  -15.1     -24.6
#> 6 homelesshomeless:polydrugmultiple drugs used  13.3      23.2
```

4.8.1.2. zero-inflation

```
library(glmmTMB)
zinf_fit1 = glmmTMB(
  family = "poisson",
  data  = needles,
  formula = shared_syr ~ age + sex + homeless*polydrug,
  ziformula = ~ age + sex + homeless + polydrug # fit won't converge with interaction
)

zinf_fit1 |>
  parameters(exponentiate = TRUE) |>
  print_md()
```

Table 4.8.: Zero-inflated poisson model

Table 4.8.: # Fixed Effects

Parameter	IRR	SE	95% CI	z	p
(Intercept)	3.16	0.82	(1.90, 5.25)	4.44	< .001
age	1.01	5.88e-03	(1.00, 1.02)	1.74	0.081
sex [F]	3.43	0.44	(2.67, 4.40)	9.68	< .001
homeless [homeless]	3.44	0.47	(2.63, 4.50)	9.03	< .001
polydrug [multiple drugs used]	1.85e-09	1.21e-05	(0.00, Inf)	-3.08e-03	0.998
homeless [homeless] × polydrug [multiple drugs used]	1.38e+08	9.04e+11	(0.00, Inf)	2.87e-03	0.998

Table 4.9.: Zero-inflated poisson model

Table 4.9.: # Zero-Inflation

Parameter	Odds Ratio	SE	95% CI	z	p
(Intercept)	0.49	0.54	(0.06, 4.25)	-0.65	0.514
age	1.05	0.03	(1.00, 1.10)	1.95	0.051
sex [F]	1.44	0.84	(0.46, 4.50)	0.62	0.533
homeless [homeless]	0.68	0.34	(0.26, 1.80)	-0.78	0.436
polydrug [multiple drugs used]	1.15	0.91	(0.24, 5.43)	0.18	0.858

Another R package for zero-inflated models is `pscl`[1] (Zeileis, Kleiber, and Jackman (2008)).

4.8.1.3. zero-inflated negative binomial model

```
library(glmmTMB)
zinf_fit1 = glmmTMB(
  family = nbinom2,
  data  = needles,
  formula = shared_syr ~ age + sex + homeless*polydrug,
  ziformula = ~ age + sex + homeless + polydrug
  # fit won't converge with interaction
)

zinf_fit1 |>
  parameters(exponentiate = TRUE) |>
  print_md()
```

Table 4.10.: Zero-inflated negative binomial model

Table 4.10.: # Fixed Effects

Parameter	IRR	SE	95% CI	z	p
(Intercept)	1.06	1.48	(0.07, 16.52)	0.04	0.969
age	1.02	0.03	(0.96, 1.08)	0.53	0.599
sex [F]	6.86	6.36	(1.12, 42.16)	2.08	0.038
homeless [homeless]	6.44	4.59	(1.60, 26.01)	2.62	0.009
polydrug [multiple drugs used]	8.25e-10	7.07e-06	(0.00, Inf)	-2.44e-03	0.998
homeless [homeless] × polydrug [multiple drugs used]	2.36e+08	2.02e+12	(0.00, Inf)	2.25e-03	0.998

[1] https://cran.r-project.org/web/packages/pscl/index.html

Table 4.11.: Zero-inflated negative binomial model

Table 4.11.: # Zero-Inflation

Parameter	Odds Ratio	SE	95% CI	z	p
(Intercept)	0.10	0.20	(1.47e-03, 6.14)	-1.11	0.269
age	1.07	0.04	(0.99, 1.15)	1.78	0.075
sex [F]	2.72	2.40	(0.48, 15.33)	1.13	0.258
homeless [homeless]	1.15	0.86	(0.27, 4.96)	0.19	0.853
polydrug [multiple drugs used]	0.75	0.86	(0.08, 7.12)	-0.25	0.799

Table 4.12.: Zero-inflated negative binomial model

Table 4.12.: # Dispersion

Parameter	Coefficient	95% CI
(Intercept)	0.44	(0.11, 1.71)

4.8.2. Quasipoisson

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

See `?quasipoisson` in R for more.

4.9. More on count regression

- https://bookdown.org/roback/bookdown-BeyondMLR/ch-poissonreg.html

5. Introduction to multi-level models for correlated data

For more, see:

- David Rocke[1]'s materials from the 2021 edition of this course[2]
  - May 25 - June 1 lectures
- Other UC Davis courses:
  - EVE 225[3]: "Linear Mixed Modeling in Ecology & Evolution"
    - usually taught every other winter or spring by Kate Laskowski[4]
    - materials, including syllabus and lecture videos: https://laskowskilab.faculty.ucdavis.edu/teaching-2/
  - STA/BST 224[5]: "Analysis of Longitudinal Data"
    - usually taught every spring by Shuai Chen[6]
    - should be accessible after completing Epi 204
  - EPI 226[7] "Methods for Longitudinal & Repeated Measurement Data"
    - usually taught by Heejung Bang[8]
  - PSC 205D[9] "Multilevel Models"
  - PSC 205G[10] "Applied Longitudinal Data Analysis"
  - STA 101[11] "Advanced Applied Statistics for the Biological Sciences"
  - STA 207[12] "Statistical Methods for Research II"
  - STA 232B[13] "Applied Statistics II"
    - usually taught every winter by Jiming Jiang[14]
  - PLS 207[15]: "Applied Statistical Modeling for the Environmental Sciences"
  - EDU 236[16]: "Application of Hierarchical Linear Models in Education Research"
  - HDE 205[17]: "Longitudinal Data Analysis"
- Books:

[1] https://dmrocke.ucdavis.edu/
[2] https://dmrocke.ucdavis.edu/Class/EPI204-Spring-2021/EPI204-Spring-2021.html
[3] https://catalog.ucdavis.edu/search/?q=EVE+225
[4] https://eve.ucdavis.edu/people/kate-laskowski
[5] https://catalog.ucdavis.edu/search/?P=BST%20224
[6] https://shuaichen.weebly.com/
[7] https://catalog.ucdavis.edu/search/?P=EPI+226
[8] https://biostat.ucdavis.edu/people/heejung-bang
[9] https://catalog.ucdavis.edu/search/?q=PSC+205D
[10] https://catalog.ucdavis.edu/search/?q=PSC+205G
[11] https://catalog.ucdavis.edu/search/?q=STA+101
[12] https://catalog.ucdavis.edu/search/?q=STA+207
[13] https://www.stat.ucdavis.edu/~jiang/sta232b.html
[14] https://www.stat.ucdavis.edu/~jiang/
[15] https://catalog.ucdavis.edu/search/?q=PLS+207
[16] https://catalog.ucdavis.edu/search/?q=EDU+236
[17] https://catalog.ucdavis.edu/search/?q=HDE+205

- Dobson and Barnett (2018) Chapter 11[18]
- Vittinghoff et al. (2012) Chapter 7[19]
- Gelman and Hill (2007)
- Jiang and Nguyen (2021)
  - by UC Davis Statistics Professor and GGE faculty member Jiming Jiang[20]
- Faraway (2016)
- McCulloch, Searle, and Neuhaus (2008)
- Hedeker and Gibbons (2006)
- Wakefield (2013)
- Zuur (2009)
- Diggle et al. (2013)
- Fitzmaurice, Laird, and Ware (2012)
- Fitzmaurice et al. (2009)
- Gałecki and Burzykowski (2013)
- Congdon (2020)
- Molenberghs and Verbeke (2005)
- Verbeke and Molenberghs (2000)
- Jewell and Hubbard (2016)
  - by UC Berkeley professors

[18] https://www.taylorfrancis.com/chapters/mono/10.1201/9781315182780-11/clustered-longitudinal-data-annette-dobson-adrian-barnett?context=ubx&refId=95f6c50e-093a-4488-a042-92a9f151a4b5
[19] https://link.springer.com/chapter/10.1007/978-1-4614-1353-0_7
[20] https://www.stat.ucdavis.edu/~jiang/

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. [21] 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.

[21] Binary outcomes are typically defined *for a specific time-point*. It is important to clearly define whether we are interested in outcome status at end of study, at end of life, or at some other time.

6. Introduction to Survival Analysis

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(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' = 6)

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 default
legend_text_size = 9
run_graphs = TRUE
```

6.1. Overview

6.1.1. 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* or *survival time analysis* might be a better name.

6.2. Time-to-event outcome distributions

6.2.1. 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.

6.2.2. 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.

6.2.3. 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.

6.3. Distribution functions for time-to-event variables

6.3.1. The Probability Density Function (PDF)

For a time-to-event variable T with a continuous distribution, the **probability density function** is defined as usual (see Section C.4.1).

In most time-to-event models, this density is assumed to be 0 for all $t < 0$; that is, $f(t) = 0, \forall t < 0$. In other words, the support of T is typically $[0, \infty)$.

Example 6.1 (exponential distribution)**.** Recall from Epi 202: the pdf of the exponential distribution family of models is:

$$p(T = t) = 1_{t \geq 0} \cdot \lambda \mathrm{e}^{-\lambda t}$$

where $\lambda > 0$.

Here are some examples of exponential pdfs:

6.3.2. The Cumulative Distribution Function (CDF)

The **cumulative distribution function** is defined as:

$$\begin{aligned} F(t) &\stackrel{\text{def}}{=} \Pr(T \leq t) \\ &= \int_{u=-\infty}^{t} f(u)du \end{aligned}$$

Example 6.2 (exponential distribution)**.** Recall from Epi 202: the cdf of the exponential distribution family of models is:

$$P(T \leq t) = \mathbb{1}_{t \geq 0} \cdot (1 - \mathrm{e}^{-\lambda t})$$

where $\lambda > 0$.

Here are some examples of exponential cdfs:

6.3.3. The Survival Function

For survival data, a more important quantity is the **survival function**:

Definition 6.1 (Survival function)**.**

Given a random time-to-event variable T, the **survival function** or **survivor function**, denoted $\mathrm{S}(t)$, is the probability that the event time is later than t. If the event in a clinical trial is death, then $\mathrm{S}(t)$ 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:

$$\mathrm{S}(t) \stackrel{\text{def}}{=} \Pr(T > t)$$

Theorem 6.1.

$$\begin{aligned} S(t) &\stackrel{def}{=} \Pr(T > t) \\ &= \int_{u=t}^{\infty} p(u)du \\ &= 1 - F(t) \end{aligned}$$

Example 6.3 (exponential distribution)**.** Since $\mathrm{S}(t) = 1 - F(t)$, the survival function of the exponential distribution family of models is:

$$P(T > t) = \begin{cases} \mathrm{e}^{-\lambda t}, t \geq 0 \\ 1, t \leq 0 \end{cases}$$

where $\lambda > 0$.

Figure 6.1 shows some examples of exponential survival functions.

```
library(ggplot2)
ggplot() +
  geom_function(
    aes(col = "0.5"),
    fun = pexp,
    args = list(lower = FALSE, rate = 0.5)
  ) +
  geom_function(
    aes(col = "p = 1"),
    fun = pexp,
    args = list(lower = FALSE, rate = 1)
  ) +
  geom_function(
    aes(col = "p = 1.5"),
    fun = pexp,
    args = list(lower = FALSE, rate = 1.5)
  ) +
  geom_function(
    aes(col = "p = 5"),
    fun = pexp,
    args = list(lower = FALSE, rate = 5)
  ) +
  theme_bw() +
  ylab("S(t)") +
  guides(col = guide_legend(title = expr(lambda))) +
  xlab("Time (t)") +
  xlim(0, 2.5) +
  theme(
    legend.position = "bottom",
    axis.title.x =
      element_text(
        angle = 0,
        vjust = 1,
        hjust = 1
      ),
    axis.title.y =
      element_text(
        angle = 0,
        vjust = 1,
        hjust = 1
      )
  )
```

Figure 6.1.: Exponential Survival Functions

Theorem 6.2. *If A_t represents survival status at time t, with $A_t = 1$ denoting alive at time t and $A_t = 0$ denoting deceased at time t, then:*

$$S(t) = \Pr(A_t = 1) = E[A_t]$$

Theorem 6.3. *If T is a nonnegative random variable, then:*

$$E[T] = \int_{t=0}^{\infty} S(t)dt$$

Proof. See https://statproofbook.github.io/P/mean-nnrvar.html or □

6.3.4. The Hazard Function

Another important quantity is the **hazard function**:

Definition 6.2 (Hazard function, hazard rate, hazard rate function)**.**

The **hazard function**, **hazard rate**, **hazard rate function**, for a random variable T at value t, typically denoted as $\mathrm{h}(t)$ [1] or $\lambda(t)$, [2] is the conditional density of T at t, given $T \geq t$. That is:

$$\lambda(t) \stackrel{\text{def}}{=} \mathrm{p}(T = t | T \geq t)$$

If T represents the time at which an event occurs, then $\lambda(t)$ is the probability that the event occurs at time t, given that it has not occurred prior to time t.

Definition 6.3 (Incidence rate)**.** Given a population of N individuals indexed by i, each with their own hazard rate $\lambda_i(t)$, the **incidence rate** for that population is the mean hazard rate:

$$\bar{\lambda}(t) \stackrel{\text{def}}{=} \frac{1}{N} \sum_{i=1}^{N} \lambda_i(t)$$

Theorem 6.4 (Incidence rate in a homogenous population)**.** *If a population of individuals indexed by i all have identical hazard rates $\lambda_i(t) = \lambda(t)$, then the **incidence rate** for that population is equal to the hazard rate:*

$$\bar{\lambda}(t) = \lambda(t)$$

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 6.5).

Lemma 6.1 (Joint probability of a variable with itself)**.**

$$p(T = t, T \geq t) = p(T = t)$$

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 $p(T = t, T \geq t) = p(T = t)$. □

---

[1] for example in Dobson and Barnett (2018), Vittinghoff et al. (2012), Klein and Moeschberger (2003), and David G. Kleinbaum and Klein (2012)

[2] for example, in Rothman et al. (2021) and Kalbfleisch and Prentice (2011)

Theorem 6.5 (Hazard equals density over survival)**.**

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

Proof.

$$\begin{aligned}
\lambda(t) &= p(T = t | T \geq t) \\
&= \frac{p(T = t, T \geq t)}{p(T \geq t)} \\
&= \frac{p(T = t)}{p(T \geq t)} \\
&= \frac{f(t)}{\mathrm{S}(t)}
\end{aligned}$$

□

Example 6.4 (exponential distribution)**.** The hazard function of the exponential distribution family of models is:

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

Figure 6.2 shows some examples of exponential hazard functions.

Figure 6.2.: 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 6.6 (transform survival to hazard)**.**

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

Proof.

$$\begin{aligned}
\lambda(t) &= \frac{f(t)}{\mathrm{S}(t)} \\
&= \frac{-S'(t)}{\mathrm{S}(t)} \\
&= -\frac{S'(t)}{\mathrm{S}(t)} \\
&= -\frac{\partial}{\partial t}\log \mathrm{S}(t) \\
&= \frac{\partial}{\partial t}\{-\log \mathrm{S}(t)\}
\end{aligned}$$

□

Definition 6.4 (hazard ratio)**.**

$$\theta(t|\tilde{x} : \tilde{x}^*) \stackrel{\text{def}}{=} \frac{\lambda(t|\tilde{x})}{\lambda(t|\tilde{x}^*)}$$

6.3.5. The Cumulative Hazard Function

Since $\lambda(t) = \frac{\partial}{\partial t}\{-\log \mathrm{S}(t)\}$ (see Theorem 6.6), we also have:

Corollary 6.1.

$$S(t) = exp\left\{-\int_{u=0}^{t} \lambda(u)du\right\} \tag{6.1}$$

The integral in Equation 6.1 is important enough to have its own name: **cumulative hazard**.

Definition 6.5 (cumulative hazard)**.** The **cumulative hazard function**, often denoted $\Lambda(t)$ or $\mathrm{H}(t)$, is defined as:

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

As we will see below, $\Lambda(t)$ 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 6.5. The cumulative hazard function for the exponential distribution with rate parameter λ is:

$$\Lambda(t) = \mathbb{1}_{t\geq 0} \cdot \lambda t$$

Figure 6.3 shows some examples of exponential cumulative hazard functions.

Figure 6.3.: Examples of exponential cumulative hazard functions

6.3.6. Some Key Mathematical Relationships among Survival Concepts

6.3.6.1. Diagram:

$$\mathrm{f}(t) \xleftarrow[\mathrm{S}(t)\lambda(t)]{-S'(t)} \mathrm{S}(t) \xleftarrow{\exp\{-\Lambda(t)\}} \Lambda(t) \xleftarrow{\int_{u=0}^{t}\lambda(u)du} \lambda(t) \xleftarrow{\exp\{\eta(t)\}} \eta(t)$$

$$\mathrm{f}(t) \xrightarrow[\int_{u=t}^{\infty}\mathrm{f}(u)du]{\mathrm{f}(t)/\lambda(t)} \mathrm{S}(t) \xrightarrow[-\log \mathrm{S}(t)]{} \Lambda(t) \xrightarrow[\Lambda'(t)]{} \lambda(t) \xrightarrow[\log\{\lambda(t)\}]{} \eta(t)$$

6.3.6.2. Identities:

$$\begin{aligned}
\mathrm{S}(t) &= 1 - \mathrm{F}(t) \\
&= \exp\{-\Lambda(t)\} \\
\mathrm{S}'(t) &= -f(t) \\
\Lambda(t) &= -\log\{\mathrm{S}(t)\} \\
\Lambda'(t) &= \lambda(t) \\
\lambda(t) &= \frac{\mathrm{f}(t)}{\mathrm{S}(t)} \\
&= -\frac{\partial}{\partial t}\log \mathrm{S}(t) \\
f(t) &= \lambda(t)\cdot \mathrm{S}(t)
\end{aligned}$$

Some proofs (others left as exercises):

$$\begin{aligned} S'(t) &= \frac{\partial}{\partial t}(1 - F(t)) \\ &= -F'(t) \\ &= -f(t) \end{aligned}$$

$$\begin{aligned} \frac{\partial}{\partial t} \log \mathrm{S}(t) &= \frac{S'(t)}{\mathrm{S}(t)} \\ &= -\frac{f(t)}{\mathrm{S}(t)} \\ &= -\lambda(t) \end{aligned}$$

$$\begin{aligned} \Lambda(t) &\stackrel{\text{def}}{=} \int_{u=0}^{t} h(u)du \\ &= \int_{0}^{t} -\frac{\partial}{\partial u} \log\left\{S(u)\right\} du \\ &= \left[-\log\left\{S(u)\right\}\right]_{u=0}^{u=t} \\ &= \left[\log\left\{S(u)\right\}\right]_{u=t}^{u=0} \\ &= \log\{\mathrm{S}(0)\} - \log\{\mathrm{S}(t)\} \\ &= \log\{1\} - \log\{\mathrm{S}(t)\} \\ &= 0 - \log\{\mathrm{S}(t)\} \\ &= -\log\{\mathrm{S}(t)\} \end{aligned}$$

Corollary:

$$\mathrm{S}(t) = \exp\left\{-\Lambda(t)\right\}$$

6.3.6.3. Example: Time to death the US in 2004

The first day is the most dangerous:

```r
# download `survexp.rda` from:
# paste0(
# "https://github.com/therneau/survival/raw/",
# "f3ac93704949ff26e07720b56f2b18ffa8066470/",
# "Data/survexp.rda")

# (newer versions of `survival` don't have the first-year breakdown; see:
# https://cran.r-project.org/web/packages/survival/news.html)

fs::path(
  here::here(),
  "Data",
  "survexp.rda"
) |>
  load()
s1 <- survexp.us[, "female", "2004"]
age1 <- c(
  0.5 / 365.25,
  4 / 365.25,
  17.5 / 365.25,
  196.6 / 365.25,
  1:109 + 0.5
)
s2 <- 365.25 * s1[5:113]
s2 <- c(s1[1], 6 * s1[2], 22 * s1[3], 337.25 * s1[4], s2)
cols <- rep(1, 113)
cols[1] <- 2
cols[2] <- 3
cols[3] <- 4

plot(age1, s1, type = "b", lwd = 2, xlab = "Age", ylab = "Daily Hazard Rate", col = cols)

text(10, .003, "First Day", col = 2)
text(18, .00030, "Rest of First Week", col = 3)
text(18, .00015, "Rest of First month", col = 4)
```

Figure 6.4.: Daily Hazard Rates in 2004 for US Females

Exercise 6.1. Hypothesize why the male and female hazard functions in Figure 6.5 differ where they do?

```
yrs <- 1:40
s1 <- survexp.us[5:113, "male", "2004"]
s2 <- survexp.us[5:113, "female", "2004"]

age1 <- 1:109

plot(age1[yrs], s1[yrs], type = "l", lwd = 2, xlab = "Age", ylab = "Daily Hazard Rate")
lines(age1[yrs], s2[yrs], col = 2, lwd = 2)
legend(5, 5e-6, c("Males", "Females"), col = 1:2, lwd = 2)
```

Figure 6.5.: Daily Hazard Rates in 2004 for US Males and Females 1-40

Exercise 6.2. Compare and contrast Figure 6.6 with Figure 6.4.

```
s1 <- survexp.us[, "female", "2004"]

s2 <- 365.25 * s1[5:113]
s2 <- c(s1[1], 6 * s1[2], 21 * s1[3], 337.25 * s1[4], s2)
cs2 <- cumsum(s2)
age2 <- c(1 / 365.25, 7 / 365.25, 28 / 365.25, 1:110)
plot(age2, exp(-cs2), type = "l", lwd = 2, xlab = "Age", ylab = "Survival")
```

Figure 6.6.: Survival Curve in 2004 for US Females

6.3.7. Likelihood with censoring

If an event time T is observed exactly as $T = t$, then the likelihood of that observation is just its probability density function:

$$\begin{aligned}
\mathcal{L}(t) &= \mathrm{f}(T = t) \\
&\stackrel{\text{def}}{=} \mathrm{f}_T(t) \\
&= \lambda_T(t)\mathrm{S}_T(t) \\
\ell(t) &\stackrel{\text{def}}{=} \log\{\mathcal{L}(t)\} \\
&= \log\{\lambda_T(t)\mathrm{S}_T(t)\} \\
&= \log\{\lambda_T(t)\} + \log\{\mathrm{S}_T(t)\} \\
&= \log\{\lambda_T(t)\} - \Lambda_T(t)
\end{aligned}$$

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:

$$\begin{aligned}
\mathcal{L}(y) &= p_T(T > y) \\
&\stackrel{\text{def}}{=} \mathrm{S}_T(y) \\
\ell(y) &\stackrel{\text{def}}{=} \log\{\mathcal{L}(y)\} \\
&= \log\{\mathrm{S}(y)\} \\
&= -\Lambda(y)
\end{aligned}$$

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 $D \stackrel{\text{def}}{=} \mathbb{1}\{T <= C\}$.

Then the complete likelihood of the observed data (Y, D) is:

$$\begin{aligned}\mathcal{L}(y, d) &= \mathrm{p}(Y = y, D = d) \\ &= [\mathrm{p}(T = y, C > y)]^d \cdot [\mathrm{p}(T > y, C = y)]^{1-d}\end{aligned}$$

Typically, survival analyses assume that C and T are mutually independent; this assumption is called "non-informative" censoring.

Then the joint likelihood $\mathrm{p}(Y, D)$ factors into the product $\mathrm{p}(Y), \mathrm{p}(D)$, and the likelihood reduces to:

$$\begin{aligned}\mathcal{L}(y, d) &= [\mathrm{p}(T = y, C > y)]^d \cdot [\mathrm{p}(T > y, C = y)]^{1-d} \\ &= [\mathrm{p}(T = y)\mathrm{p}(C > y)]^d \cdot [\mathrm{p}(T > y)\mathrm{p}(C = y)]^{1-d} \\ &= [\mathrm{f}_T(y)\mathrm{S}_C(y)]^d \cdot [\mathrm{S}(y)\mathrm{f}_C(y)]^{1-d} \\ &= [\mathrm{f}_T(y)^d\mathrm{S}_C(y)^d] \cdot [\mathrm{S}_T(y)^{1-d}\mathrm{f}_C(y)^{1-d}] \\ &= (\mathrm{f}_T(y)^d \cdot \mathrm{S}_T(y)^{1-d}) \cdot (\mathrm{f}_C(y)^{1-d} \cdot \mathrm{S}_C(y)^d)\end{aligned}$$

The corresponding log-likelihood is:

$$\begin{aligned}\ell(y, d) &= \log\{\mathcal{L}(y, d)\} \\ &= \log\{(f_T(y)^d \cdot S_T(y)^{1-d}) \cdot (f_C(y)^{1-d} \cdot S_C(y)^d)\} \\ &= \log\{f_T(y)^d \cdot S_T(y)^{1-d}\} + \log\{f_C(y)^{1-d} \cdot S_C(y)^d\}\end{aligned}$$

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.

The corresponding score function is:

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

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:

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

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:

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

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:

$$\begin{aligned}
\ell(y,d) &= \log\{\mathcal{L}(y,d)\} \\
&= \log\{S_T(y) \cdot h_T(y)^d\} \\
&= \log\{S_T(y)\} + \log\{h_T(y)^d\} \\
&= \log\{S_T(y)\} + d \cdot \log\{h_T(y)\} \\
&= -H_T(y) + d \cdot \log\{h_T(y)\}
\end{aligned}$$

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.

6.4. Parametric Models for Time-to-Event Outcomes

6.4.1. 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}

6.4.1.1. Mathematical details of exponential distribution

$$
\begin{aligned}
f(t) &= \lambda \mathrm{e}^{-\lambda t} \\
F(t) &= 1 - \mathrm{e}^{-\lambda t} \\
\mathrm{S}(t) &= \mathrm{e}^{-\lambda t} \\
\ln(\mathrm{S}(t)) &= -\lambda t \\
\lambda(t) &= -\frac{f(t)}{\mathrm{S}(t)} = -\frac{\lambda \mathrm{e}^{-\lambda t}}{\mathrm{e}^{-\lambda t}} = \lambda \\
E(t) &= \lambda^{-1} \\
Var(t) &= \lambda^{-2} \\
\log\{f(t)\} &= \log\{\lambda\} - \lambda t \\
\frac{\partial}{\partial \lambda} \log\{f(t)\} &= \lambda^{-1} - t \\
&= \mathrm{E}[t] - t \\
&= -(\mathrm{E}[t] - t) \\
&= -\varepsilon
\end{aligned}
$$

6.4.1.2. Prediction intervals for time-to-event outcomes

Exercise 6.3 (Construct a prediction interval)**.** Suppose a cancer patient is predicted to have an expected (mean) lifetime of 7 years after diagnosis, and suppose the distribution is exponential.

Construct a 95% prediction interval for survival.

> Tip
>
> Use the quantiles of the exponential distribution.

Solution 6.1. If the mean is 7 years until death, then the rate parameter $\lambda = 1/7$ events (deaths) per year.

The 0.025 quantile of the exponential distribution with $\lambda = 1/7$ is `qexp(p 0.025, rate = 1/7)` $= 0.177225$ and the 0.975 quantile is `qexp(p 0.975, rate = 1/7)` $= 25.822156$, so the prediction interval is `qexp(p c(.025, 0.975), rate = 1/7)` $= (0.177225, 25.822156)$.

Exercise 6.4. Graph the prediction interval as a function of the mean, for Gaussian ($\sigma = 1$), Binomial, Poisson, and Exponential.

Solution 6.2. Left to the reader for now.

Exercise 6.5 (Explain the results)**.** Why do time-to-event models have such wide predictive intervals?

> **Tip**
>
> Consider the relationship between the mean, variance, and standard deviation of the exponential distribution, and contrast that relationship with the Poisson distribution and the Bernoulli distribution.

Solution 6.3. In the exponential distribution, variance is the square of the mean (hence SD is equal to mean); as opposed to Poisson, where variance was equal to the mean (and SD is the square-root of the mean), or the Bernoulli, where the variance is the mean minus the square of the mean (so the SD is smaller than the square-root of the mean).

6.4.1.3. Estimating λ

- Suppose we have m exponential survival times of $t_1, t_2, \dots, t_m$ and k right-censored values at $u_1, u_2, \dots, u_k$.
- 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 $t_1, t_2, \dots, t_m$ and k right-censored values at $u_1, u_2, \dots, u_k$. The log-likelihood of an observed survival time t_i is

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

and the likelihood of a censored value is the probability of that outcome (survival greater than u_j) so the log-likelihood is

$$\begin{aligned}\ell_j(\lambda) &= \log\left\{\lambda e^{u_j}\right\} \\ &= -\lambda u_j\end{aligned}$$

Theorem 6.7. *Let $T = \sum t_i$ and $U = \sum u_j$. Then:*

$$\hat{\lambda}_{ML} = \frac{m}{T+U} \tag{6.2}$$

Proof.

$$\begin{aligned}\ell(\lambda) &= \sum_{i=1}^{m}(\ln\lambda - \lambda t_i) + \sum_{j=1}^{k}(-\lambda u_j) \\ &= m\ln\lambda - (T+U)\lambda \\ \ell'(\lambda) &= m\lambda^{-1} - (T+U) \\ \hat{\lambda} &= \frac{m}{T+U}\end{aligned}$$

□

$$\begin{aligned}\ell'' &= -m/\lambda^2 \\ &< 0 \\ \hat{E}[T] &= \hat{\lambda}^{-1} \\ &= \frac{T+U}{m}\end{aligned}$$

6.4.1.4. Fisher Information and Standard Error

$$
\begin{aligned}
E[-\ell''] &= m/\lambda^2 \\
\operatorname{Var}\left(\hat{\lambda}\right) &\approx \left(E[-\ell'']\right)^{-1} \\
&= \lambda^2/m \\
\operatorname{SE}\left(\hat{\lambda}\right) &= \sqrt{\operatorname{Var}\left(\hat{\lambda}\right)} \\
&\approx \lambda/\sqrt{m}
\end{aligned}
$$

$\hat{\lambda}$ depends on the censoring times of the censored observations, but $\operatorname{Var}\left(\hat{\lambda}\right)$ only depends on the number of uncensored observations, m, and not on the number of censored observations (k).

6.4.2. Other Parametric Survival Distributions

- Any density on $[0, \infty)$ can be a survival distribution, but the most useful ones are all skew right.
- The most frequently used 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 semi-parametric, but sometimes these parametric distributions provide a useful approach.

6.5. Nonparametric Survival Analysis

6.5.1. 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.

6.6. Example: clinical trial for pediatric acute leukemia

6.6.1. 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.

6.6.2. 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 (`remstat`)
- `remstat` = 1: partial
- `remstat` = 2: complete
- randomized to 6-MP (exit time: `t2`) or placebo (`t1`).
- Followed until relapse or end of study.
- All of the placebo group relapsed,
- Some of the 6-MP group were censored.

6.6.3. Data documentation for `drug6mp`

```
# library(printr) # inserts help-file output into markdown output
library(KMsurv)
?drug6mp
```

6.6.4. 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.

Table 6.1.: `drug6mp` pediatric acute leukemia data

```
library(KMsurv)
data(drug6mp)
drug6mp <- drug6mp |>
  tibble::as_tibble() |>
  print()
#> # A tibble: 21 x 5
#>     pair remstat    t1    t2 relapse
#>    <int>   <int> <int> <int>   <int>
#>  1     1       1     1    10       1
#>  2     2       2    22     7       1
#>  3     3       2     3    32       0
#>  4     4       2    12    23       1
#>  5     5       2     8    22       1
#>  6     6       1    17     6       1
#>  7     7       2     2    16       1
#>  8     8       2    11    34       0
#>  9     9       2     8    32       0
#> 10    10       2    12    25       0
#> # i 11 more rows
```

Table 6.2.: Summary statistics for `drug6mp` data

```
summary(drug6mp)
#>       pair       remstat           t1              t2          relapse
#>  Min.   : 1   Min.   :1.00   Min.   : 1.00   Min.   : 6.0   Min.   :0.000
#>  1st Qu.: 6   1st Qu.:2.00   1st Qu.: 4.00   1st Qu.: 9.0   1st Qu.:0.000
#>  Median :11   Median :2.00   Median : 8.00   Median :16.0   Median :0.000
#>  Mean   :11   Mean   :1.76   Mean   : 8.67   Mean   :17.1   Mean   :0.429
#>  3rd Qu.:16   3rd Qu.:2.00   3rd Qu.:12.00   3rd Qu.:23.0   3rd Qu.:1.000
#>  Max.   :21   Max.   :2.00   Max.   :23.00   Max.   :35.0   Max.   :1.000
```

6.6.5. Exponential model

- We *can* compute the hazard rate, assuming an exponential model: number of relapses divided by the sum of the exit times (Equation 6.2).

$$\hat{\lambda} = \frac{\sum_{i=1}^{n} D_i}{\sum_{i=1}^{n} Y_i}$$

- For the placebo, that is just the reciprocal of the mean time:

$$\begin{aligned}
\hat{\lambda}_{\text{placebo}} &= \frac{\sum_{i=1}^{n} D_i}{\sum_{i=1}^{n} Y_i} \\
&= \frac{\sum_{i=1}^{n} 1}{\sum_{i=1}^{n} Y_i} \\
&= \frac{n}{\sum_{i=1}^{n} Y_i} \\
&= \frac{1}{\bar{Y}} \\
&= \frac{1}{8.666667} \\
&= 0.115385
\end{aligned}$$

- For the 6-MP group, $\hat{\lambda} = 9/359 = 0.025$

$$\begin{aligned}
\hat{\lambda}_{\text{6-MP}} &= \frac{\sum_{i=1}^{n} D_i}{\sum_{i=1}^{n} Y_i} \\
&= \frac{9}{359} \\
&= 0.02507
\end{aligned}$$

- The estimated hazard in the placebo group is 4.6 times as large as in the 6-MP group (assuming the hazard is constant over time).

6.7. The Kaplan-Meier Product Limit Estimator

6.7.1. Estimating survival in datasets without censoring

In the `drug6mp` dataset, the estimated survival function for the placebo patients is easy to compute. For any time t in months, $\mathrm{S}(t)$ is the fraction of patients with times greater than t:

6.7.2. Estimating survival in datasets with censoring

- 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

$$\frac{Y-d}{Y} = 1 - \frac{d}{Y}$$

Definition 6.6 (Kaplan-Meier Product-Limit Estimator of Survival Function)**.** If a time-to-event data set contains k event times t_i, $(i \in 1:k)$, where n_i is the number of individuals at risk at time t_i and d_i is the number of events at time t_i, then the **Kaplan-Meier Product-Limit Estimator** of the survival function is:

$$\hat{\lambda}_i = \frac{d_i}{n_i}$$

$$\hat{\mathrm{S}}_{KM}(t) \stackrel{\text{def}}{=} \prod_{\{i:\ t_i<t\}} \left[1 - \hat{\lambda}_i\right]$$

Theorem 6.8 (Kaplan-Meier Estimate with No Censored Observations)**.** *If there are no censored data, and there are n data points, then just after (say) the third event time*

$$\begin{aligned}
\hat{S}(t) &= \prod_{t_i<t} \left[1 - \frac{d_i}{Y_i}\right] \\
&= \left[\frac{n-d_1}{n}\right]\left[\frac{n-d_1-d_2}{n-d_1}\right]\left[\frac{n-d_1-d_2-d_3}{n-d_1-d_2}\right] \\
&= \frac{n-d_1-d_2-d_3}{n} \\
&= 1 - \frac{d_1+d_2+d_3}{n} \\
&= 1 - \hat{F}(t)
\end{aligned}$$

where $\hat{F}(t)$ is the usual empirical CDF estimate.

6.7.3. 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):

```
# | echo: false

require(KMsurv)
data(drug6mp)
library(dplyr)
library(survival)

drug6mp_km_model1 <-
  drug6mp |>
  mutate(surv = Surv(t2, relapse)) |>
  survfit(formula = surv ~ 1, data = _)

library(ggfortify)
drug6mp_km_model1 |>
  autoplot(
    mark.time = TRUE,
    conf.int = FALSE
  ) +
  expand_limits(y = 0) +
  xlab("Time since diagnosis (months)") +
  ylab("KM Survival Curve")
```

Figure 6.7.: Kaplan-Meier Survival Curve for 6-MP Patients

6.7.4. 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 Factor` = 1 - Hazard,
    `Cumulative Hazard` = cumsum(`Hazard`),
    `KM Survival Curve` = cumprod(`KM Factor`)
```

```
  )

library(pander)
pander(km.6mp)
```

t2	Relapses	Censored	Exiting	Study Size	Exited	At Risk	Hazard	KM Factor	Cumulative Hazard	KM Survival Curve
0	0	0	0	21	0	21	0	1	0	1
6	3	1	4	21	0	21	0.1429	0.8571	0.1429	0.8571
7	1	0	1	21	4	17	0.05882	0.9412	0.2017	0.8067
9	0	1	1	21	5	16	0	1	0.2017	0.8067
10	1	1	2	21	6	15	0.06667	0.9333	0.2683	0.7529
11	0	1	1	21	8	13	0	1	0.2683	0.7529
13	1	0	1	21	9	12	0.08333	0.9167	0.3517	0.6902
16	1	0	1	21	10	11	0.09091	0.9091	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	0.1429	0.8571	0.5854	0.5378
23	1	0	1	21	15	6	0.1667	0.8333	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

6.7.4.1. 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 $0.857 \times 0.941 = 0.807$. 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)
```

Figure 6.8.: KM curve for 6MP patients, calculated by hand

6.8. 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).

6.8.1. 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.

6.8.1.1. Example: `Surv()` with `drug6mp` data

```
library(survival)
drug6mp.v3 <-
  drug6mp.v2 |>
```

```
4   mutate(
5     surv2 = Surv(
6       time = t2,
7       event = (outcome == "relapsed")
8     )
9   )
10
11 print(drug6mp.v3)
12 #> # A tibble: 21 x 7
13 #>     pair remstat     t1    t2 relapse outcome   surv2
14 #>    <int> <chr>    <int> <int>   <int> <chr>    <Surv>
15 #>  1     1 partial      1    10       1 relapsed    10
16 #>  2     2 complete    22     7       1 relapsed     7
17 #>  3     3 complete     3    32       0 censored    32+
18 #>  4     4 complete    12    23       1 relapsed    23
19 #>  5     5 complete     8    22       1 relapsed    22
20 #>  6     6 partial     17     6       1 relapsed     6
21 #>  7     7 complete     2    16       1 relapsed    16
22 #>  8     8 complete    11    34       0 censored    34+
23 #>  9     9 complete     8    32       0 censored    32+
24 #> 10    10 complete    12    25       0 censored    25+
25 #> # i 11 more rows
```

The output of `Surv()` is a vector of objects with class `Surv`. When we print this vector:

- observations where the event was observed are printed as the event time (for example, `surv2 = 10` on line 1)
- observations where the event was right-censored are printed as the censoring time with a plus sign (`+`; for example, `surv2 = 32+` on line 3).

6.8.2. 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.

6.8.2.1. 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:

```
print(drug6mp.km_model)
#> Call: survfit(formula = surv2 ~ 1, data = drug6mp.v3)
#>
#>       n events median 0.95LCL 0.95UCL
#> [1,] 21      9     23      16      NA
```

`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
#>    16     11       1    0.627  0.1141        0.439        0.896
#>    22      7       1    0.538  0.1282        0.337        0.858
#>    23      6       1    0.448  0.1346        0.249        0.807
```

We can specify which time points we want using the `times` argument:

```
summary(
  drug6mp.km_model,
  times = c(0, drug6mp.v3$t2)
)
#> Call: survfit(formula = surv2 ~ 1, data = drug6mp.v3)
#>
#>  time n.risk n.event survival std.err lower 95% CI upper 95% CI
#>     0     21       0    1.000  0.0000        1.000        1.000
#>    10     15       1    0.753  0.0963        0.586        0.968
#>     7     17       1    0.807  0.0869        0.653        0.996
#>    32      4       0    0.448  0.1346        0.249        0.807
#>    23      6       1    0.448  0.1346        0.249        0.807
#>    22      7       1    0.538  0.1282        0.337        0.858
#>     6     21       3    0.857  0.0764        0.720        1.000
#>    16     11       1    0.627  0.1141        0.439        0.896
#>    34      2       0    0.448  0.1346        0.249        0.807
#>    32      4       0    0.448  0.1346        0.249        0.807
#>    25      5       0    0.448  0.1346        0.249        0.807
```

```
#>    11      13        0     0.753  0.0963         0.586         0.968
#>    20       8        0     0.627  0.1141         0.439         0.896
#>    19       9        0     0.627  0.1141         0.439         0.896
#>     6      21        3     0.857  0.0764         0.720         1.000
#>    17      10        0     0.627  0.1141         0.439         0.896
#>    35       1        0     0.448  0.1346         0.249         0.807
#>     6      21        3     0.857  0.0764         0.720         1.000
#>    13      12        1     0.690  0.1068         0.510         0.935
#>     9      16        0     0.807  0.0869         0.653         0.996
#>     6      21        3     0.857  0.0764         0.720         1.000
#>    10      15        1     0.753  0.0963         0.586         0.968
```

```
?summary.survfit
```

6.8.3. Plotting estimated survival functions

We can plot `survfit` objects with `plot()`, `autoplot()`, or `ggsurvplot()`:

```
library(ggfortify)
autoplot(drug6mp.km_model)
```

Figure 6.9.: Kaplan-Meier Survival Curve for 6-MP Patients

```
# not shown:
# plot(drug6mp.km_model)
```

```
# library(survminer)
# ggsurvplot(drug6mp.km_model)
```

6.8.3.1. 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())
#> # A tibble: 2 x 4
#>       p quantile lower upper
#>   <dbl>    <dbl> <dbl> <dbl>
#> 1  0.25       13     6    NA
#> 2  0.5        23    16    NA
```

6.9. The log-rank test

(a.k.a. the Mantel-Cox test)

Exercise 6.6. How do we test the null hypothesis that two or more groups have the same time-to-event distribution?

Solution 6.4. One option is the log-rank test comparing the Kaplan-Meier estimates of the survival functions of those groups.

Adapted from David G. Kleinbaum and Klein (2012) p68:

- The log–rank test is a large-sample chi-square test.
- The log–rank test uses a test statistic that compares KM curves between groups across all survival times.
- Like many other statistics used in other kinds of chi-square tests, the log–rank statistic makes use of observed versus expected cell counts over categories of outcomes.
- The categories for the log–rank statistic are defined by each of the ordered failure times for the entire set of data being analyzed.

For $t \in t_1, ..., t_n$:

$$\hat{\lambda}_t = \frac{\sum_x m_{x,t}}{\sum_x n_{x,t}}$$
$$\hat{E}_{t,x} = \hat{\lambda}_t * n_{x,t}$$

6.9.1. The `survdiff` function

```
?survdiff
```

6.9.2. 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)
library(tidyr)
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:

```
o_e_summ <- o_e |>
  summarize(
    across(starts_with("expected"), sum),
    across(starts_with("n_events_"), sum)
  )
pander::pander(o_e_summ)
```

Table 6.4.: Observed and expected event counts for the 6-MP data, for log-rank test

```
o_e <- drug6mp.v4 |>
  arrange(exit_time) |>
  mutate(
    .by = treatment,
    n_exited = row_number(),
    n_at_risk = n() - n_exited + 1
  ) |>
  dplyr::summarize(
    .by = all_of(c("exit_time", "treatment")),
    n_at_risk = max(n_at_risk),
    n_events = sum(outcome == "relapsed")
  ) |>
  tidyr::pivot_wider(
    names_from = "treatment",
    values_from = c(n_at_risk, n_events)
  ) |>
  tidyr::fill(
    starts_with("n_at_risk"),
    .direction = "up"
  ) |>
  replace_na(list("n_events_placebo" = 0,
                  "n_events_6-MP" = 0)) |>
  mutate(
    n_at_risk = rowSums(across(starts_with("n_at_risk"))),
    n_events = rowSums(across(starts_with("n_events"))),
    marginal_hazard = n_events / n_at_risk,
    expected_6mp = marginal_hazard * `n_at_risk_6-MP`,
    expected_plc = marginal_hazard * n_at_risk_placebo,
    diff_6mp = `n_events_6-MP` - expected_6mp,
    diff_plc = n_events_placebo - expected_plc
  ) |>
  filter(n_events > 0)

o_e
#> # A tibble: 17 x 12
#>    exit_time n_at_risk_placebo `n_at_risk_6-MP` n_events_placebo `n_events_6-MP`
#>        <int>             <dbl>            <dbl>            <int>           <int>
#>  1         1                21               21                2               0
#>  2         2                19               21                2               0
#>  3         3                17               21                1               0
#>  4         4                16               21                2               0
#>  5         5                14               21                2               0
#>  6         6                12               21                0               3
#>  7         7                12               17                0               1
#>  8         8                12               16                4               0
#>  9        10                 8               15                0               1
#> 10        11                 8               13                2               0
#> 11        12                 6               12                2               0
#> 12        13                 4               12                0               1
#> 13        15                 4               11                1               0
#> 14        16                 3               11                0               1
#> 15        17                 3               10                1               0
```

Table 6.5.: Observed and expected sums for the 6-MP data, for log-rank test

expected_6mp	expected_plc	n_events_placebo	n_events_6-MP
19.25	10.75	21	9

The exact variance formula for each of two groups is:

$$\mathrm{Var}(O_i - E_i) = \sum_j \frac{n_{1j} n_{2j} (m_j)(n_j - m_j)}{(n_j)^2 (n_j - 1)}$$

See David G. Kleinbaum and Klein (2012), Chapter 2 Appendix for the exact variance formula for more than two groups.

Or we can use an approximate statistic:

$$X^2 \approx \sum_{i=1}^{p} \frac{(O_i - E_i)^2}{E_i}$$

```
with(
  o_e_summ,
  tibble(
    "6mp" = (`n_events_6-MP` - expected_6mp)^2 / expected_6mp,
    "placebo" = (n_events_placebo - expected_plc)^2 / expected_plc,
    sum = `6mp` + placebo
  )
) |>
  pander::pander()
```

6mp	placebo	sum
5.458	9.775	15.23

R gives us both the exact and approximate results:

```
survdiff(
  formula = surv ~ treatment,
  data = drug6mp.v4
)
#> Call:
#> survdiff(formula = surv ~ treatment, data = drug6mp.v4)
#>
```

```
#>                     N Observed Expected (O-E)^2/E (O-E)^2/V
#> treatment=6-MP    21        9     19.3      5.46      16.8
#> treatment=placebo 21       21     10.7      9.77      16.8
#>
#>  Chisq= 16.8  on 1 degrees of freedom, p= 4e-05
```

By default, `survdiff()` ignores any pairing, but we can use `strata()` to perform something similar to a paired t-test:

```
lrank_test <- survdiff(
  formula = surv ~ treatment + strata(pair),
  data = drug6mp.v4
)
lrank_test
#> Call:
#> survdiff(formula = surv ~ treatment + strata(pair), data = drug6mp.v4)
#>
#>                     N Observed Expected (O-E)^2/E (O-E)^2/V
#> treatment=6-MP    21        9     16.5      3.41      10.7
#> treatment=placebo 21       21     13.5      4.17      10.7
#>
#>  Chisq= 10.7  on 1 degrees of freedom, p= 0.001
```

Interestingly, accounting for pairing reduces the significance of the difference.

6.10. Example: Bone Marrow Transplant Data

Data from Copelan et al. (1991)

Figure 1.1 *Recovery Process from a Bone Marrow Transplant*

Figure 6.10.: Recovery process from a bone marrow transplant (Fig. 1.1 from Klein and Moeschberger (2003))

6.10.1. Study design

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.

6.10.2. `KMsurv::bmt` data in R

```
library(KMsurv)
?bmt
```

6.10.3. 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.

6.10.4. Survival Function Estimate and Variance

$$\hat{\mathrm{S}}(t) = \prod_{t_i < t} \left[1 - \frac{d_i}{Y_i} \right]$$

where Y_i is the group at risk at time t_i.

The estimated variance of $\hat{\mathrm{S}}(t)$ is:

Theorem 6.9 (Greenwood's estimator for variance of Kaplan-Meier survival estimator)**.**

$$\widehat{Var}\big(\hat{S}(t)\big) = \hat{S}(t)^2 \sum_{t_i < t} \frac{d_i}{Y_i(Y_i - d_i)} \tag{6.3}$$

We can use Equation 6.3 for confidence intervals for a survival function or a difference of survival functions.

Kaplan-Meier survival curves

```r
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
)
```

```r
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 6.11.: Disease-Free Survival by Disease Group

6.10.5. 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 $\text{Bin}(Y_i, p_i)$. Letting $\text{S}(t)$ be the "true" survival function

$$\hat{\text{S}}(t) = \prod_{t_i < t} x_i / Y_i$$
$$\text{S}(t) = \prod_{t_i < t} p_i$$

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

$$
\begin{aligned}
\mathrm{Var}\left(\frac{\hat{\mathrm{S}}(t)}{\mathrm{S}(t)}\right) &\approx \mathrm{Var}\left(1+\sum_{t_i<t}\frac{\hat{p}_i-p_i}{p_i}\right) \\
&= \sum_{t_i<t}\frac{1}{p_i^2}\frac{p_i(1-p_i)}{Y_i} \\
&= \sum_{t_i<t}\frac{(1-p_i)}{p_iY_i} \\
&\approx \sum_{t_i<t}\frac{(1-x_i/Y_i)}{x_i} \\
&= \sum_{t_i<t}\frac{Y_i-x_i}{x_iY_i} \\
&= \sum_{t_i<t}\frac{d_i}{Y_i(Y_i-d_i)} \\
\therefore \mathrm{Var}\big(\hat{\mathrm{S}}(t)\big) &\approx \hat{\mathrm{S}}(t)^2\sum_{t_i<t}\frac{d_i}{Y_i(Y_i-d_i)}
\end{aligned}
$$

6.10.6. 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 freedom, p= 0.001
```

6.10.7. Cumulative Hazard

$$
\begin{aligned}
\lambda(t) &\stackrel{\text{def}}{=} \mathrm{p}(T=t|T\geq t) \\
&= \frac{\mathrm{p}(T=t)}{\mathrm{P}(T\geq t)} \\
&= -\frac{\partial}{\partial t}\log\{\mathrm{S}(t)\}
\end{aligned}
$$

The **cumulative hazard** (or **integrated hazard**) function is

$$
\Lambda(t) \stackrel{\text{def}}{=} \int_0^t \lambda(t)dt
$$

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

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

So we can estimate $\Lambda(t)$ as:

$$\begin{aligned}\hat{\Lambda}(t) &= -\log\left\{\hat{\mathrm{S}}(t)\right\} \\ &= -\log\left\{\prod_{t_i<t}\left[1-\frac{d_i}{Y_i}\right]\right\} \\ &= -\sum_{t_i<t}\log\left\{1-\frac{d_i}{Y_i}\right\}\end{aligned}$$

This is the **Kaplan-Meier (product-limit) estimate of cumulative hazard**.

6.10.7.1. 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 6.12.: Disease-Free Cumulative Hazard by Disease Group

6.11. Nelson-Aalen Estimates of Cumulative Hazard and Survival

---

Definition 6.7 (Nelson-Aalen Cumulative Hazard Estimator)**.**

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**:

$$\hat{\Lambda}_{NA}(t) \stackrel{\text{def}}{=} \sum_{\{i:\ t_i<t\}} \hat{\lambda}_i$$

Theorem 6.10 (Variance of Nelson-Aalen estimator)**.**

The variance of this estimator is approximately:

$$\begin{aligned} \hat{Var}\left(\hat{H}_{NA}(t)\right) &= \sum_{t_i<t} \frac{(d_i/Y_i)(1-d_i/Y_i)}{Y_i} \\ &\approx \sum_{t_i<t} \frac{d_i}{Y_i^2} \end{aligned} \tag{6.4}$$

Since $\mathrm{S}(t) = \exp\{-\Lambda(t)\}$, the Nelson-Aalen cumulative hazard estimate can be converted into an alternate estimate of the survival function:

$$\begin{aligned}\hat{S}_{NA}(t) &= \exp\left\{-\hat{H}_{NA}(t)\right\} \\ &= \exp\left\{-\sum_{t_i<t}\frac{d_i}{Y_i}\right\} \\ &= \prod_{t_i<t}\exp\left\{-\frac{d_i}{Y_i}\right\}\end{aligned}$$

Compare these with the corresponding Kaplan-Meier estimates:

$$\begin{aligned}\hat{H}_{KM}(t) &= -\sum_{t_i<t}\log\left\{1-\frac{d_i}{Y_i}\right\} \\ \hat{S}_{KM}(t) &= \prod_{t_i<t}\left[1-\frac{d_i}{Y_i}\right]\end{aligned}$$

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.

6.11.1. Application to `bmt` dataset

```
na_fit <- survfit(
  formula = surv ~ group,
  type = "fleming-harrington",
  data = bmt
)

km_fit <- survfit(
  formula = surv ~ group,
  type = "kaplan-meier",
  data = bmt
)

km_and_na <-
  bind_rows(
    .id = "model",
    "Kaplan-Meier" = km_fit |> fortify(surv.connect = TRUE),
    "Nelson-Aalen" = na_fit |> fortify(surv.connect = TRUE)
  ) |>
  as_tibble()
```

```
km_and_na |>
  ggplot(aes(x = time, y = surv, col = model)) +
  geom_step() +
  facet_grid(. ~ strata) +
  theme_bw() +
  ylab("S(t) = P(T>=t)") +
  xlab("Survival time (t, days)") +
  theme(legend.position = "bottom")
```

Figure 6.13.: 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.

7. Proportional Hazards 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(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' = 6)

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 default
legend_text_size = 9
run_graphs = TRUE
```

7.1. Introduction

Exercise 7.1. Recall the key characteristics of the exponential distribution:

- density function $\mathrm{f}(t)$
- survival function $\mathrm{S}(t)$
- hazard function $\lambda(t)$

Solution 7.1.

$$\begin{aligned}\mathrm{p}(t) &= \lambda e^{-\lambda t}\\ \mathrm{S}(t) &= e^{-\lambda t}\\ \lambda(t) &= \lambda\end{aligned}$$

Note that the exponential distribution has **constant hazard**.

7.2. Understanding proportional hazards models

Let's make two generalizations. First, we let the hazard depend on some covariates $x_1, x_2, \dots, x_p$; we will indicate this dependence by extending our notation for hazard:

Definition 7.1 (conditional hazard)**.** The **conditional hazard** of outcome T at value t, given covariate vector $\tilde{x}$, is the conditional density of the event $T = t$, given $T \geq t$ and $\tilde{X} = \tilde{x}$:

$$\lambda(t|\tilde{x}) \stackrel{\text{def}}{=} \mathrm{p}(T = t | T \geq t, \tilde{X} = \tilde{x}) \tag{7.1}$$

Definition 7.2 (baseline hazard)**.**

The **baseline hazard**, **base hazard**, or **reference hazard**, denoted $\lambda_0(t)$ or $\lambda_0(t)$, is the hazard function for the subpopulation of individuals whose covariates are all equal to their reference levels:

$$\lambda_0(t) \stackrel{\text{def}}{=} \lambda(t|\tilde{X} = \tilde{0}) \tag{7.2}$$

The baseline hazard is *somewhat* analogous to the intercept term in linear regression, but it is **not** a mean.

Similarly:

Definition 7.3 (baseline cumulative hazard)**.**

The **baseline cumulative hazard**, **base cumulative hazard**, or **reference cumulative hazard**, denoted $H_0(t)$ or $\Lambda_0(t)$, is the cumulative hazard function (Definition 6.5) for the subpopulation of individuals whose covariates are all equal to their reference levels:

$$\Lambda_0(t) \stackrel{\text{def}}{=} \Lambda(t|\tilde{X} = \tilde{0}) \tag{7.3}$$

Also:

Definition 7.4 (Baseline survival function)**.** The **baseline survival function** is the survival function for an individual whose covariates are all equal to their default values.

$$\mathrm{S}_0(t) \stackrel{\text{def}}{=} \mathrm{S}(t|\tilde{X} = \tilde{0})$$

Now, let's define ***how*** the hazard function depends on covariates. We typically use a log link to model the relationship between the hazard function, $\lambda(t|\tilde{x})$, and the linear component, $\eta(t|\tilde{x})$, as we did for Poisson models in Chapter 4; that is:

Definition 7.5 (log-hazard)**.**

The **log-hazard** function, denoted $\eta(t)$, is the natural logarithm of the hazard function:

$$\eta(t) \stackrel{\text{def}}{=} \log\{\lambda(t)\}$$

Definition 7.6 (conditional log-hazard)**.**

The **conditional log-hazard** function, denoted $\eta(t|\tilde{x})$, is the natural logarithm of the conditional hazard function:

$$\eta(t|\tilde{x}) \stackrel{\text{def}}{=} \log\{\lambda(t|\tilde{x})\}$$

In contrast with Poisson regression, here $\eta(t|\tilde{x})$ depends on **both** t **and** $\tilde{x}$.

Definition 7.7 (baseline log-hazard)**.**

The **baseline log-hazard**, denoted $\eta_0(t)$, log-hazard function for the subpopulation of individuals whose covariates are all equal to their reference levels:

$$\eta_0(t) \stackrel{\text{def}}{=} \eta(t|\tilde{X} = \tilde{0})$$

Theorem 7.1.

$$\lambda(t|\tilde{x}) = exp\{\eta(t|\tilde{x})\}$$

Definition 7.8 (difference in log-hazards)**.** The **difference in log-hazards** between covariate patterns $\tilde{x}$ and $\tilde{x}^*$ at time t is:

$$\Delta\eta(t|\tilde{x} : \tilde{x}^*) \stackrel{\text{def}}{=} \eta(t|\tilde{x}) - \eta(t|\tilde{x}^*)$$

Theorem 7.2 (Difference of log-hazards vs hazard ratio)**.** *If $\Delta\eta(t|\tilde{x} : \tilde{x}^*)$ is the difference in log-hazard between covariate patterns $\tilde{x}$ and $\tilde{x}^*$ at time t, and $\theta(t|\tilde{x} : \tilde{x}^*)$ is corresponding hazard ratio, then:*

$$\Delta\eta(t|\tilde{x} : \tilde{x}^*) = log\{\theta(t|\tilde{x} : \tilde{x}^*)\}$$

Proof. Using Definition 6.4:

$$\begin{aligned}
\Delta\eta(t|\tilde{x} : \tilde{x}^*) &\stackrel{\text{def}}{=} \eta(t|\tilde{x}) - \eta(t|\tilde{x}^*) \\
&= \log\{\lambda(t|\tilde{x})\} - \log\{\lambda(t|\tilde{x}^*)\} \\
&= \log\left\{\frac{\lambda(t|\tilde{x})}{\lambda(t|\tilde{x}^*)}\right\} \\
&= \log\{\theta(t|\tilde{x} : \tilde{x}^*)\}
\end{aligned}$$

□

Corollary 7.1 (Hazard ratio vs difference of log-odds)**.**

$$\theta(t|\tilde{x} : \tilde{x}^*) = exp\{\Delta\eta(t|\tilde{x} : \tilde{x}^*)\}$$

Definition 7.9 (difference in log-hazard from baseline)**.**

The difference in log-hazard for covariate pattern $\tilde{x}$ compared to the baseline covariate pattern $\tilde{0}$ is:

$$\Delta\eta(t|\tilde{x}) \stackrel{\text{def}}{=} \Delta\eta(t|\tilde{x} : \tilde{0})$$

Theorem 7.3 (Decomposition of log-hazard)**.**

$$\eta(t|\tilde{x}) = \eta_0(t) + \Delta\eta(t|\tilde{x})$$

Definition 7.10 (Hazard ratio versus baseline)**.**

$$\theta(t|\tilde{x}) \stackrel{\text{def}}{=} \theta(t|\tilde{x} : \tilde{0}) \tag{7.4}$$

Corollary 7.2.

$$\theta(t|\tilde{x}) = exp\{\Delta\eta(t|\tilde{x})\}$$

Proof.

$$\begin{aligned}\theta(t|\tilde{x}) &\stackrel{\text{def}}{=} \theta(t|\tilde{x} : \tilde{0}) \\ &= \exp\{\Delta\eta(t|\tilde{x})\}\end{aligned}$$

□

Corollary 7.3.

$$\Delta\eta(t|\tilde{x}) = log\{\theta(t|\tilde{x})\}$$

As the second generalization, we let the base hazard, cumulative hazard, and survival functions depend on t, but not on any covariates (for now). We can do this using either parametric or semi-parametric approaches.

Definition 7.11 (Proportional hazards model)**.** A **proportional hazards** model for a time-to-event outcome T is a model where the difference in log-hazard from the baseline log-hazard is equal to a linear combination of the predictors:

$$\Delta\eta(t|\tilde{x}) = \tilde{x} \cdot \tilde{\beta} \tag{7.5}$$

Equivalently:

Lemma 7.1. *In a proportional hazards model (that is, if Equation 7.5 holds):*

$$\begin{aligned} \eta(t|\tilde{x}) &= \eta_0(t) + \tilde{x} \cdot \tilde{\beta} \\ &= \eta_0(t) + \beta_1 x_1 + \cdots + \beta_p x_p \end{aligned} \tag{7.6}$$

In a proportional hazards model, the baseline log-hazard is analogous to the intercept term in a generalized linear model, except that the baseline log-hazard depends on time, t.

Lemma 7.2. *If $\eta(t|\tilde{x}) = \eta_0(t) + \tilde{x} \cdot \tilde{\beta}$, then:*

$$\Delta\eta(t|\tilde{x} : \tilde{x}^*) = (\tilde{x} - \tilde{x}^*) \cdot \beta$$

Theorem 7.4. *If $\eta(t|\tilde{x}) = \eta_0(t) + \tilde{x} \cdot \tilde{\beta}$, then:*

$$\begin{aligned} \theta(t|\tilde{x} : \tilde{x}^*) &= exp\{\Delta\eta(t|\tilde{x} : \tilde{x}^*)\} \\ &= exp\{(\tilde{x} - \tilde{x}^*) \cdot \beta\} \end{aligned}$$

So for proportional hazards models, we can write the hazard ratio using a shorthand notation:

$$\theta(t|\tilde{x} : \tilde{x}^*) = \theta(\tilde{x} : \tilde{x}^*)$$

Lemma 7.3.

$$\Delta\eta(t|\tilde{x}) = \tilde{x} \cdot \tilde{\beta} \tag{7.7}$$

Theorem 7.5. *If* $\eta(t|\tilde{x}) = \eta_0(t) + \tilde{x} \cdot \tilde{\beta}$, *then:*

$$\theta(t|\tilde{x}) = exp\Big\{\tilde{x} \cdot \tilde{\beta}\Big\}$$

Proof.

$$\begin{aligned}\theta(t|\tilde{x}) &\stackrel{\text{def}}{=} \theta(t|\tilde{x} : \tilde{0}) \\ &= \exp\{\Delta\eta(t|\tilde{x})\} \\ &= \exp\Big\{\tilde{x} \cdot \tilde{\beta}\Big\}\end{aligned}$$

□

Theorem 7.6.

$$\lambda(t|x) = \lambda_0(t)\theta(x)$$

Also:

Theorem 7.7.

$$\begin{aligned}\theta(x) &= exp\{\Delta\eta(x)\} \\ \log\lambda(t|x) &= \log\lambda_0(t) + \Delta\eta(x) \\ &= \eta_0(t) + \Delta\eta(x) \\ \Delta\eta(x) &= \tilde{x} \cdot \tilde{\beta} \\ &\stackrel{def}{=} \beta_1 x_1 + \cdots + \beta_p x_p\end{aligned}$$

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 $\beta_0(t) = \log\lambda_0(t)$, and then:

$$\eta(x,t) = \beta_0(t) + \beta_1 x_1 + \cdots + \beta_p x_p$$

For two different individuals with covariate patterns $\tilde{x}_1$ and $\tilde{x}_2$, the ratio of the hazard functions (a.k.a. **hazard ratio**, a.k.a. **relative hazard**) is:

$$\begin{aligned}\frac{\lambda(t|\tilde{x}_1)}{\lambda(t|\tilde{x}_2)} &= \frac{\lambda_0(t)\theta(\tilde{x}_1)}{\lambda_0(t)\theta(\tilde{x}_2)} \\ &= \frac{\theta(\tilde{x}_1)}{\theta(\tilde{x}_2)}\end{aligned}$$

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 7.12 (proportional hazards)**.** A conditional probability distribution $p(T|X)$ has **proportional hazards** if the hazard ratio $\lambda(t|\tilde{x}_1)/\lambda(t|\tilde{x}_2)$ does not depend on t. Mathematically, it can be written as:

$$\frac{\lambda(t|\tilde{x}_1)}{\lambda(t|\tilde{x}_2)} = \theta(\tilde{x}_1, \tilde{x}_2)$$

As we saw above, Cox's proportional hazards model has this property, with $\theta(\tilde{x}_1, \tilde{x}_2) = \frac{\theta(\tilde{x}_1)}{\theta(\tilde{x}_2)}$.

Theorem 7.8.

We are using two similar notations, $\theta(\tilde{x}, \tilde{x}^*)$ and $\theta(\tilde{x})$. We can link these notations:

$$\theta(\tilde{x}) \stackrel{def}{=} \theta(\tilde{x}, \tilde{0})$$

Then:

$$\begin{aligned}\theta(\tilde{x}, \tilde{x}^*) &= \frac{\theta(\tilde{x})}{\theta(\tilde{x}^*)} \\ \theta(\tilde{0}) = \theta(\tilde{0}, \tilde{0}) &= 1\end{aligned}$$

The proportional hazards model also has additional notable properties:

$$\begin{aligned}\frac{\lambda(t|\tilde{x}_1)}{\lambda(t|\tilde{x}_2)} &= \frac{\theta(\tilde{x}_1)}{\theta(\tilde{x}_2)} \\ &= \frac{\exp\{\eta(\tilde{x}_1)\}}{\exp\{\eta(\tilde{x}_2)\}} \\ &= \exp\{\eta(\tilde{x}_1) - \eta(\tilde{x}_2)\} \\ &= \exp\{\tilde{x}_1'\beta - \tilde{x}_2'\beta\} \\ &= \exp\{(\tilde{x}_1 - \tilde{x}_2)'\beta\}\end{aligned}$$

Hence on the log scale, we have:

Theorem 7.9.

$$\begin{aligned}\log \frac{\lambda(t|\tilde{x})}{\lambda(t|\tilde{x}^*)} &= \Delta\eta(t|\tilde{x} : \tilde{x}^*) \\ &\stackrel{def}{=} \eta(t|\tilde{x}) - \eta(t|\tilde{x}^*) \\ &= \eta(\tilde{x}_1) - \eta(\tilde{x}_2) \\ &= \tilde{x}_1'\beta - \tilde{x}_2'\beta \\ &= (\tilde{x}_1 - \tilde{x}_2)'\beta\end{aligned}$$

If only one covariate x_j is changing, then:

$$\begin{aligned}\log \frac{\lambda(t|\tilde{x}_1)}{\lambda(t|\tilde{x}_2)} &= (x_{1j} - x_{2j}) \cdot \beta_j \\ &\propto (x_{1j} - x_{2j})\end{aligned}$$

That is, under Cox's model $\lambda(t|\tilde{x}) = \lambda_0(t)\exp\{\tilde{x}'\beta\}$, the log of the hazard ratio is proportional to the difference in x_j, with the proportionality coefficient equal to β_j.

Further,

$$\log \lambda(t|\tilde{x}) = \log \lambda_0(t) + x'\beta$$

That is, the covariate effects are additive on the log-hazard scale; hazard functions for different covariate patterns should be vertical shifts of each other.

See also:

https://en.wikipedia.org/wiki/Proportional_hazards_model#Why_it_is_called_%22proportional%22

7.2.1. Additional properties of the proportional hazards model

If $\lambda(t|x) = \lambda_0(t)\theta(x)$, then:

Theorem 7.10 (Cumulative hazards are also proportional to $\Lambda_0(t)$)**.**

$$\begin{aligned}\Lambda(t|x) &\stackrel{def}{=} \int_{u=0}^{t} \lambda(u)du \\ &= \int_{u=0}^{t} \lambda_0(u)\theta(x)du \\ &= \theta(x)\int_{u=0}^{t} \lambda_0(u)du \\ &= \theta(x)\Lambda_0(t)\end{aligned}$$

where $\Lambda_0(t) \stackrel{def}{=} \Lambda(t|0) = \int_{u=0}^{t} \lambda_0(u)du$.

Theorem 7.11 (The logarithms of cumulative hazard should be parallel)**.**

$$log\{\Lambda(t|\tilde{x})\} = log\{\Lambda_0(t)\} + \tilde{x} \cdot \tilde{\beta}$$

Corollary 7.4 (linear model for log-negative-log survival)**.**

$$log\{-log\{S(t|\tilde{x})\}\} = log\{-log\{S_0(t)\}\} + \tilde{x} \cdot \tilde{\beta}$$

Theorem 7.12 (Survival functions are exponential multiples of $\mathrm{S}_0(t)$)**.**

$$S(t|x) = [S_0(t)]^{\theta(x)}$$

Proof.

$$\begin{aligned}\mathrm{S}(t|x) &= \exp\{-\Lambda(t|x)\} \\ &= \exp\{-\theta(x) \cdot \Lambda_0(t)\} \\ &= (\exp\{-\Lambda_0(t)\})^{\theta(x)} \\ &= [\mathrm{S}_0(t)]^{\theta(x)}\end{aligned}$$

□

7.2.2. Summary of proportional hazards model structure and assumptions

Joint likelihood of data set: $\mathcal{L} \stackrel{\text{def}}{=} \mathrm{p}(\tilde{Y} = \tilde{y}, \tilde{D} = \tilde{d} | \mathbf{X} = \mathbf{x})$

Marginal likelihood contribution of obs. $\boldsymbol{i}$: $\mathcal{L}_i \stackrel{\text{def}}{=} \mathrm{p}(Y_i = y_i, D_i = d_i | \tilde{X}_i = \tilde{x}_i)$

Independent Observations Assumption: $\mathcal{L} = \prod_{i=1}^{n} \mathcal{L}_i$

Non-Informative Censoring Assumption: $T_i \perp\!\!\!\perp C_i | \tilde{X}_i$

$$\mathcal{L}_i \propto [\mathrm{f}_T(y_i|\tilde{x}_i)]^{d_i} [\mathrm{S}_T(y_i|\tilde{x}_i)]^{1-d_i} = \mathrm{S}_T(y_i|\tilde{x}_i) \cdot [\lambda_T(y_i|\tilde{x}_i)]^{d_i}$$

Survival function: $\mathrm{S}(t|\tilde{x}) \stackrel{\text{def}}{=} \mathrm{P}(T > t | \tilde{X} = \tilde{x}) = \int_{u=t}^{\infty} \mathrm{f}(u|\tilde{x}) du = \exp\{-\Lambda(t|\tilde{x})\}$

Probability density function: $\mathrm{f}(t|\tilde{x}) \stackrel{\text{def}}{=} \mathrm{p}(T = t | \tilde{X} = \tilde{x}) = -\mathrm{S}'(t|\tilde{x}) = \lambda(t|\tilde{x})\mathrm{S}(t|\tilde{x})$

Cumulative hazard function: $\Lambda(t|\tilde{x}) \stackrel{\text{def}}{=} \int_{u=0}^{t} \lambda(u|\tilde{x}) du = -\log\{\mathrm{S}(t|\tilde{x})\}$

Hazard function: $\lambda(t|\tilde{x}) \stackrel{\text{def}}{=} \mathrm{p}(T = t | T \geq t, \tilde{X} = \tilde{x}) = \Lambda'(t|\tilde{x}) = \frac{\mathrm{f}(t|\tilde{x})}{\mathrm{S}(t|\tilde{x})}$

Hazard ratio: $\theta(t|\tilde{x} : \tilde{x}^*) \stackrel{\text{def}}{=} \frac{\lambda(t|\tilde{x})}{\lambda(t|\tilde{x}^*)}$

Log-Hazard function: $\eta(t|\tilde{x}) \stackrel{\text{def}}{=} \log\{\lambda(t|\tilde{x})\} = \eta_0(t) + \Delta\eta(t|\tilde{x})$

Proportional Hazards Assumption:

$$\begin{aligned} \lambda(t|\tilde{x}) &= \lambda_0(t) \cdot \theta(\tilde{x}) \\ \Lambda(t|\tilde{x}) &= \Lambda_0(t) \cdot \theta(\tilde{x}) \\ \eta(t|\tilde{x}) &= \eta_0(t) + \Delta\eta(\tilde{x}) \end{aligned}$$

Logarithmic Link Function Assumption:

- **Link function**:

$$\log\{\lambda(t|\tilde{x})\} = \eta(t|\tilde{x})$$
$$\log\{\theta(\tilde{x})\} = \Delta\eta(\tilde{x})$$

- **Inverse link function**:

$$\lambda(t|\tilde{x}) = \exp\{\eta(t|\tilde{x})\}$$
$$\theta(\tilde{x}) = \exp\{\Delta\eta(\tilde{x})\}$$

Linear Predictor Component:

$$\eta(t|\tilde{x}) = \eta_0(t) + \Delta\eta(t|\tilde{x})$$
$$\Delta\eta(t|\tilde{x}) = \tilde{x} \cdot \tilde{\beta}$$

Linear Predictor Component Functional Form Assumption:

$$\Delta\eta(t|\tilde{x}) = \tilde{x} \cdot \tilde{\beta} \stackrel{\text{def}}{=} \beta_1 x_1 + \cdots + \beta_p x_p$$

7.3. 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)
library(dplyr)
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)))
sf2 <- with(nafit[2], stepfun(time,c(1,surv)))
sf3 <- with(nafit[3], stepfun(time,c(1,surv)))

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(
    aes(
      x = timevec,
      y = cumhaz1/cumhaz2)
  ) +
  geom_line(aes(col = "ALL/Low Risk AML")) +
  ylab("Hazard Ratio") +
  xlab("Time") +
```

```
  ylim(0,6) +
  geom_line(aes(y = cumhaz3/cumhaz1, col = "High Risk AML/ALL")) +
  geom_line(aes(y = cumhaz3/cumhaz2, col = "High Risk AML/Low Risk AML")) +
  theme_bw() +
  labs(colour = "Comparison") +
  theme(legend.position="bottom")

print(bmt_rel_hazard_plot)
```

Figure 7.1.: Hazard Ratios by Disease Group for `bmt` data

We can zoom in on the first 300 days to take a closer look:

```
bmt_rel_hazard_plot + xlim(c(0,300))
```

Figure 7.2.: Hazard Ratios by Disease Group (0-300 Days)

The cumulative hazard curves should also be proportional

```
library(ggfortify)
plot_cuhaz_bmt =
  bmt |>
  survfit(formula = Surv(t2, d3) ~ group) |>
  autoplot(fun = "cumhaz",
           mark.time = TRUE) +
  ylab("Cumulative hazard")

plot_cuhaz_bmt |> print()
```

Figure 7.3.: Disease-Free Cumulative Hazard by Disease Group

```
plot_cuhaz_bmt +
  scale_y_log10() +
  scale_x_log10()
```

Figure 7.4.: Disease-Free Cumulative Hazard by Disease Group (log-scale)

7.3.1. 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"?

```
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 7.5.: Smoothed Hazard Rate Estimates by Disease Group

Group 3 was plotted first because it has the highest hazard.

Except for an initial blip in the high risk AML group, the hazards look roughly proportional. They are all strongly decreasing.

7.4. Fitting proportional hazards models to data

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 $\lambda_0(t)$. For the covariates, supposing for simplicity that there are no tied event times, let the event times for the whole data set be $t_1, t_2, \dots, t_D$. Let the risk set at time t_i be $R(t_i)$ and

$$\begin{aligned}
\eta(\tilde{x}) &= \beta_1 x_1 + \cdots + \beta_p x_p \\
\theta(\tilde{x}) &= e^{\eta(\tilde{x})} \\
\lambda(t|X = x) &= \lambda_0(t) e^{\eta(\tilde{x})} = \theta(\tilde{x})\lambda_0(t)
\end{aligned}$$

Conditional on a single failure at time t, the probability that the event is due to subject $f \in R(t)$ is approximately

$$\begin{aligned}
\Pr(f \text{ fails}|1 \text{ failure at } t) &= \frac{\lambda_0(t) e^{\eta(\tilde{x}_f)}}{\sum_{k \in R(t)} \lambda_0(t) e^{\eta(\tilde{x}_f)}} \\
&= \frac{\theta(\tilde{x}_f)}{\sum_{k \in R(t)} \theta(\tilde{x}_k)}
\end{aligned}$$

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_j 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

$$\begin{aligned}
\mathcal{L}_i^* &= \frac{\theta(\tilde{x}_i)}{\sum_{k \in R(t_i)} \theta(\tilde{x}_k)} \\
\mathcal{L}^* &= \prod_{\{i:\ d_i = 1\}} \mathcal{L}_i^*
\end{aligned}$$

and we can numerically maximize this with respect to the coefficients $\tilde{\beta}$ that specify $\eta(\tilde{x}) = \tilde{x}'\tilde{\beta}$. 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 $\hat{\tilde{\beta}} = (\hat{\beta}_1, \dots, \hat{\beta}_p)$, this also defines $\hat{\eta}(x)$ and $\hat{\theta}(x)$, and then the estimated base cumulative hazard function is

$$\hat{\Lambda}_0(t) = \sum_{t_i < t} \frac{d_i}{\sum_{k \in R(t_i)} \theta(x_k)}$$

which reduces to the Nelson-Aalen estimate when there are no covariates. There are numerous other estimates that have been proposed as well.

7.5. Example: Proportional hazards model for the `bmt` data

7.5.1. Fit the model

```
library(survival)
bmt.cox <- coxph(Surv(t2, d3) ~ group, data = bmt)
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     1.467    0.267  1.43    0.152
#> ---
#> Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
#>
#>                     exp(coef) exp(-coef) lower .95 upper .95
#> groupLow Risk AML       0.563      1.776     0.321     0.989
#> groupHigh Risk AML      1.467      0.682     0.869     2.478
#>
#> Concordance= 0.625  (se = 0.03 )
#> Likelihood ratio test= 13.4  on 2 df,   p=0.001
#> Wald test            = 13  on 2 df,   p=0.001
#> Score (logrank) test = 13.8  on 2 df,   p=0.001
```

The table provides hypothesis tests comparing groups 2 and 3 to group 1. Group 3 has the highest hazard, so the most significant comparison is not directly shown.

The coefficient 0.3834 is on the log-hazard-ratio scale, as in log-risk-ratio. The next column gives the hazard ratio 1.4673, and a hypothesis (Wald) test.

The (not shown) group 3 vs. group 2 log hazard ratio is $0.3834 + 0.5742 = 0.9576$. The hazard ratio is then $\exp(0.9576)$ or 2.605.

Inference on all coefficients and combinations can be constructed using `coef(bmt.cox)` and `vcov(bmt.cox)` as with logistic and poisson regression.

Concordance is agreement of first failure between pairs of subjects and higher predicted risk between those subjects, omitting non-informative pairs.

The Rsquare value is Cox and Snell's pseudo R-squared and is not very useful.

7.5.2. Tests for nested models

`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.

7.5.3. Survival Curves from the Cox Model

We can take a look at the resulting group-specific curves:

```
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
```

Figure 7.6.: Survival Functions for Three Groups by KM and Cox Model

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.

From `?survfit.coxph`:

> 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?

7.5.4. Examining `survfit`

```
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       1    0.947  0.0362        0.879        1.000
#>    74     36       1    0.921  0.0437        0.839        1.000
#>    86     35       1    0.895  0.0498        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       1    0.816  0.0629        0.701        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
#>   172     27       1    0.684  0.0754        0.551        0.849
#>   192     26       1    0.658  0.0770        0.523        0.827
#>   194     25       1    0.632  0.0783        0.495        0.805
#>   230     23       1    0.604  0.0795        0.467        0.782
#>   276     22       1    0.577  0.0805        0.439        0.758
#>   332     21       1    0.549  0.0812        0.411        0.734
#>   383     20       1    0.522  0.0817        0.384        0.709
#>   418     19       1    0.494  0.0819        0.357        0.684
#>   466     18       1    0.467  0.0818        0.331        0.658
#>   487     17       1    0.439  0.0815        0.305        0.632
#>   526     16       1    0.412  0.0809        0.280        0.605
#>   609     14       1    0.382  0.0803        0.254        0.577
#>   662     13       1    0.353  0.0793        0.227        0.548
#>
#>                 group=Low Risk 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
#>
#>                 group=High Risk AML
#>  time n.risk n.event survival 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
#>   456     15       1    0.311  0.0690        0.201        0.481
#>   467     14       1    0.289  0.0676        0.183        0.457
#>   625     13       1    0.267  0.0659        0.164        0.433
#>   677     12       1    0.244  0.0641        0.146        0.409
```

```
survfit(bmt.cox)
#> Call: survfit(formula = bmt.cox)
#>
#>        n events median 0.95LCL 0.95UCL
#> [1,] 137     83    422     268      NA
survfit(bmt.cox, newdata = tibble(group = unique(bmt$group)))
#> Call: survfit(formula = bmt.cox, newdata = tibble(group = unique(bmt$group)))
```

```
#>
#>     n events median 0.95LCL 0.95UCL
#> 1 137     83    422     268      NA
#> 2 137     83     NA     625      NA
#> 3 137     83    268     162     467
```

```
bmt.cox |>
  survfit(newdata = tibble(group = unique(bmt$group))) |>
  summary()
#> Call: survfit(formula = bmt.cox, newdata = tibble(group = unique(bmt$group)))
#>
#>  time n.risk n.event survival1 survival2 survival3
#>     1    137       1     0.993     0.996     0.989
#>     2    136       1     0.985     0.992     0.978
#>    10    135       1     0.978     0.987     0.968
#>    16    134       1     0.970     0.983     0.957
#>    32    133       1     0.963     0.979     0.946
#>    35    132       1     0.955     0.975     0.935
#>    47    131       2     0.941     0.966     0.914
#>    48    129       2     0.926     0.957     0.893
#>    53    127       1     0.918     0.953     0.882
#>    55    126       1     0.911     0.949     0.872
#>    63    125       1     0.903     0.944     0.861
#>    64    124       1     0.896     0.940     0.851
#>    74    123       2     0.881     0.931     0.830
#>    76    121       1     0.873     0.926     0.819
#>    79    120       1     0.865     0.922     0.809
#>    80    119       2     0.850     0.913     0.788
#>    84    117       1     0.843     0.908     0.778
#>    86    116       1     0.835     0.903     0.768
#>    93    115       1     0.827     0.899     0.757
#>   100    114       1     0.820     0.894     0.747
#>   104    113       1     0.812     0.889     0.737
#>   105    112       2     0.797     0.880     0.717
#>   107    110       1     0.789     0.875     0.707
#>   109    109       1     0.782     0.870     0.697
#>   110    108       1     0.774     0.866     0.687
#>   113    107       1     0.766     0.861     0.677
#>   115    106       1     0.759     0.856     0.667
#>   120    105       1     0.751     0.851     0.657
#>   122    104       2     0.735     0.841     0.637
#>   129    102       1     0.727     0.836     0.627
#>   157    101       1     0.720     0.831     0.617
#>   162    100       1     0.712     0.826     0.607
#>   164     99       1     0.704     0.821     0.598
#>   168     98       1     0.696     0.815     0.588
#>   172     97       1     0.688     0.810     0.578
#>   183     96       1     0.680     0.805     0.568
#>   192     95       1     0.672     0.800     0.558
#>   194     94       1     0.664     0.794     0.549
```

```
#>   211     93       1     0.656     0.789     0.539
#>   219     92       1     0.648     0.783     0.530
#>   230     90       1     0.640     0.778     0.520
#>   242     89       1     0.632     0.773     0.511
#>   248     88       1     0.624     0.767     0.501
#>   268     87       1     0.616     0.761     0.492
#>   272     86       1     0.608     0.756     0.482
#>   273     85       1     0.600     0.750     0.473
#>   276     84       1     0.592     0.745     0.464
#>   288     83       1     0.584     0.739     0.454
#>   318     82       1     0.576     0.733     0.445
#>   332     81       1     0.568     0.727     0.436
#>   363     80       1     0.560     0.722     0.427
#>   381     79       1     0.552     0.716     0.418
#>   383     78       1     0.544     0.710     0.409
#>   390     77       2     0.528     0.698     0.392
#>   414     75       1     0.520     0.692     0.383
#>   418     74       1     0.512     0.686     0.374
#>   421     73       1     0.504     0.680     0.366
#>   422     72       1     0.496     0.674     0.357
#>   456     71       1     0.488     0.667     0.349
#>   466     70       1     0.480     0.661     0.340
#>   467     69       1     0.472     0.655     0.332
#>   481     68       1     0.464     0.649     0.324
#>   486     67       1     0.455     0.642     0.315
#>   487     66       1     0.447     0.636     0.307
#>   526     65       1     0.439     0.629     0.299
#>   606     63       1     0.431     0.623     0.291
#>   609     62       1     0.423     0.616     0.283
#>   625     61       1     0.415     0.609     0.275
#>   641     60       1     0.407     0.603     0.267
#>   662     59       1     0.399     0.596     0.260
#>   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
```

7.6. Adjustment for Ties (optional)

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

$$\bar{\eta}_i = \beta_1 s_{i1} + \cdots + \beta_p s_{ip}$$

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

$$\begin{aligned}
\bar{\eta}_i &= \sum_{j \in D_i} \beta_1 x_{j1} + \cdots + \beta_p x_{jp} \\
&= \beta_1 s_{i1} + \cdots + \beta_p s_{ip} \\
\bar{\theta}_i &= \exp\{\bar{\eta}_i\} \\
&= \prod_{j \in D_i} \theta_i
\end{aligned}$$

7.6.0.1. Breslow's method for ties

Breslow's method estimates the partial likelihood as

$$\begin{aligned}
L(\beta|T) &= \prod_i \frac{\bar{\theta}_i}{[\sum_{k \in R(t_i)} \theta_k]^{d_i}} \\
&= \prod_i \prod_{j \in D_i} \frac{\theta_j}{\sum_{k \in R(t_i)} \theta_k}
\end{aligned}$$

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.

7.6.0.2. 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.

7.6.0.3. 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.

7.6.0.4. 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.

$$\left(\frac{\theta_1}{\theta_R+\theta_1+\theta_2+\theta_3}\right)\left(\frac{\theta_2}{\theta_R+2(\theta_1+\theta_2+\theta_3)/3}\right)\left(\frac{\theta_3}{\theta_R+(\theta_1+\theta_2+\theta_3)/3}\right)$$

7.7. Building Cox Proportional Hazards models

7.7.1. `hodg` Lymphoma Data Set from `KMsurv`

7.7.1.1. Participants

43 bone marrow transplant patients at Ohio State University (Avalos 1993)

7.7.1.2. 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.

7.7.1.3. Data

```r
library(dplyr)
library(survival)
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     90    24    28
#>  2 Allogenic Non-Hodgkins    32 dead     30     7    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
```

7.7.2. Proportional hazards model

7.8. Diagnostic graphs for proportional hazards assumption

7.8.1. Analysis plan

- **survival function** for the four combinations of disease type and graft type.

Table 7.1.: Summary of Proportional Hazards model for Hodgkins Lymphoma data

```
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 **
#> score                         -0.0495    0.9517   0.0124 -3.98  6.8e-05 ***
#> wtime                         -0.0166    0.9836   0.0102 -1.62   0.1046
#> gtypeAutologous:dtypeHodgkins -2.3709    0.0934   1.0355 -2.29   0.0220 *
#> ---
#> Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
#>
#>                               exp(coef) exp(-coef) lower .95 upper .95
#> gtypeAutologous                  1.8953     0.5276    0.5920     6.068
#> dtypeHodgkins                   15.8050     0.0633    2.4682   101.207
#> score                            0.9517     1.0507    0.9288     0.975
#> wtime                            0.9836     1.0167    0.9641     1.003
#> gtypeAutologous:dtypeHodgkins    0.0934    10.7074    0.0123     0.711
#>
#> Concordance= 0.776  (se = 0.059 )
#> Likelihood ratio test= 32.1  on 5 df,   p=6e-06
#> Wald test            = 27.2  on 5 df,   p=5e-05
#> Score (logrank) test = 37.7  on 5 df,   p=4e-07
```

- **observed (nonparametric) vs. expected (semiparametric) survival** functions.
- **complementary log-log survival** for the four groups.

7.8.2. Kaplan-Meier survival functions

```
km_model = survfit(
  formula = surv ~ dtype + gtype,
  data = hodg2)

library(ggplot2)
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 7.7.: Kaplan-Meier Survival Curves for HOD/NHL and Allo/Auto Grafts

7.8.3. 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 7.8.: Observed and expected survival curves for `bmt` data

7.8.4. 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 7.9.: 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 7.10.: 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 7.11.: Observed and expected cumulative hazard curves for `bmt` data (cloglog format)

7.9. Predictions and Residuals

7.9.1. Review: Predictions in Linear Regression

- In linear regression, we have a linear predictor for each data point i

$$
\begin{aligned}
\eta_i &= \beta_0 + \beta_1 x_{1i} + \cdots + \beta_p x_{pi} \\
\hat{y}_i &= \hat{\eta}_i = \hat{\beta}_0 + \hat{\beta}_1 x_{1i} + \cdots + \hat{\beta}_p x_{pi} \\
y_i &\sim N(\eta_i, \sigma^2)
\end{aligned}
$$

- $\hat{y}_i$ 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.

7.9.2. 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.

7.9.3. 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:

$$\hat{\mathrm{E}}[T|X = x] = \int_{t=0}^{\infty} \hat{\mathrm{S}}(t)dt$$

7.9.4. 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)` = 0.126589 years, or 1/40 of the mean lifetime.
- The upper end is at the 0.975 point which is `qexp(.975, rate = 1/5)` = 18.444397 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!

7.9.5. 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 (Section 7.10)
  - **martingale residuals** for non-linearity
  - **dfbeta** for influence.

7.9.6. 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_{jk} 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
```

7.9.6.1. `gtype`

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

7.9.6.2. dtype

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

7.9.6.3. score

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

7.9.6.4. `wtime`

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

7.9.6.5. `gtype:dtype`

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

7.9.6.6. 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.

7.10. Goodness of Fit using the Cox-Snell Residuals

(references: Klein and Moeschberger (2003), §11.2, and Dobson and Barnett (2018), §10.6)

Suppose that an individual has a survival time T which has survival function $\mathrm{S}(t)$, meaning that $\Pr(T > t) = \mathrm{S}(t)$. Then $S(T)$ has a uniform distribution on $(0, 1)$:

$$\begin{aligned}\Pr(S(T_i) \leq u) &= \Pr(T_i > S_i^{-1}(u)) \\ &= S_i(S_i^{-1}(u)) \\ &= u\end{aligned}$$

Also, if U has a uniform distribution on $(0, 1)$, then what is the distribution of $-\ln(U)$?

$$\begin{aligned}\Pr(-\ln(U) < x) &= \Pr(U > \exp\{-x\}) \\ &= 1 - e^{-x}\end{aligned}$$

which is the CDF of an exponential distribution with parameter $\lambda = 1$.

Definition 7.13 (Cox-Snell generalized residuals)**.**

The **Cox-Snell generalized residuals** are defined as:

$$r_i^{CS} \stackrel{\text{def}}{=} \hat{\Lambda}(t_i|\tilde{x}_i)$$

If the estimate $\hat{S}_i$ is accurate, r_i^{CS} should have an exponential distribution with constant hazard $\lambda = 1$, which means that these values should look like a censored sample from this exponential distribution.

```
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 7.12.: 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.

7.11. 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.

7.11.1. 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 7.13.: 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 7.14.: 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 `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
#> 3     1  154.  6.61  0.0102
#> 4     1  152.  4.97  0.0258
```

The new model has better (lower) AIC.

7.12. 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.

7.12.1. Deviance Residuals

$$r_i^D = \text{sign}(r_i^M)\sqrt{-2\left[r_i^M + \delta_i \ln(\delta_i - r_i^M)\right]}$$
$$r_i^D = \text{sign}(r_i^M)\sqrt{-2\left[r_i^M + \delta_i \ln(r_i^{CS})\right]}$$

Roughly centered on 0 with approximate standard deviation 1.

7.12.2.

```
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 7.15.: 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 7.16.: Deviance Residuals vs. Linear Predictor

The two largest deviance residuals are observations 1 and 29. Worth examining.

7.12.3. 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.

7.12.3.1. Graft type

```
plot(hodg.dfb[,1],xlab="Observation Order",ylab="dfbeta for Graft Type")
```

Figure 7.17.: dfbeta Values by Observation Order for Graft Type

The smallest dfbeta for graft type is observation 1.

7.12.3.2. Disease type

```
plot(hodg.dfb[,2],
     xlab="Observation Order",
     ylab="dfbeta for Disease Type")
```

Figure 7.18.: dfbeta Values by Observation Order for Disease Type

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

7.12.3.3. Karnofsky score

```
plot(hodg.dfb[,3],
     xlab="Observation Order",
     ylab="dfbeta for Karnofsky Score")
```

Figure 7.19.: 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.

7.12.3.4. Waiting time (dichotomized)

```
plot(
  hodg.dfb[,4],
  xlab="Observation Order",
  ylab="dfbeta for `Waiting Time < 80`")
```

Figure 7.20.: 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.

7.12.3.5. Interaction: graft type and disease type

```
plot(hodg.dfb[,5],
     xlab="Observation Order",
     ylab="dfbeta for dtype:gtype")
```

Figure 7.21.: dfbeta Values by Observation Order for dtype:gtype

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

Table 7.2.: 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.

7.12.4.

```
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       p
#> gtypeAutologous                 0.6651    1.9447   0.5943  1.12  0.2631
#> dtypeHodgkins                   2.3273   10.2505   0.7332  3.17  0.0015
#> score                          -0.0550    0.9464   0.0123 -4.46 8.2e-06
#> wt2long                        -2.0598    0.1275   1.0507 -1.96  0.0499
#> gtypeAutologous:dtypeHodgkins -2.0668    0.1266   0.9258 -2.23  0.0256
#>
#> Likelihood ratio test=35.5  on 5 df, p=1.21e-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        79 dead     70    71 high risk grp, short wait, po~
#> 4 Autologous Non-Hodgkins    53 dead     90    17 early death, good score, med ~
#> 5 Autologous Hodgkins        30 dead     90    73 early death, good score, med ~
```

7.12.5. 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 7.3.: Linear Risk Predictors for Lymphoma

	linear.predictor
Non-Hodgkins,Allogenic	0
Non-Hodgkins,Autologous	0.6651
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.

7.13. Stratified survival models

7.13.1. 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 David G. Kleinbaum and Klein (2012) (e.g., p281):

```
anderson =
  paste0(
    "http://web1.sph.emory.edu/dkleinb/allDatasets/",
    "surv2datasets/anderson.dta") |>
  haven::read_dta() |>
  dplyr::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)
```

7.13.2. Cox semi-parametric proportional hazards model

```
anderson.cox1 = coxph(
  formula = surv ~ rx + sex + logwbc,
  data = anderson)

summary(anderson.cox1)
#> Call:
#> coxph(formula = surv ~ rx + sex + logwbc, data = anderson)
#>
#>   n= 42, number of events= 30
#>
#>           coef exp(coef) se(coef)     z Pr(>|z|)
#> rxnew   -1.504     0.222    0.462 -3.26   0.0011 **
#> sexmale  0.315     1.370    0.455  0.69   0.4887
#> logwbc   1.682     5.376    0.337  5.00  5.8e-07 ***
#> ---
#> Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 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
```

```
#> Wald test            = 33.5  on 3 df,   p=2e-07
#> Score (logrank) test = 48  on 3 df,   p=2e-10
```

7.13.2.1. 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
```

7.13.2.2. 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.

7.13.3. 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 7.22.: Cumulative hazard (cloglog scale) for `anderson` data

This can be fixed by using strata or possibly by other model alterations.

7.13.4. The Stratified Cox Model

- In a stratified Cox model, each stratum, defined by one or more factors, has its own base survival function $\lambda_0(t)$.
- 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 *
#> logwbc  1.454     4.279    0.344  4.22  2.4e-05 ***
#> ---
#> Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
#>
#>        exp(coef) exp(-coef) lower .95 upper .95
#> rxnew      0.369      2.713     0.146     0.932
#> logwbc     4.279      0.234     2.180     8.398
#>
#> Concordance= 0.812  (se = 0.059 )
#> Likelihood ratio test= 32.1  on 2 df,   p=1e-07
#> Wald test            = 22.8  on 2 df,   p=1e-05
#> Score (logrank) test = 30.8  on 2 df,   p=2e-07
```

Let's compare this to a model fit only on the subset of males:

```
anderson.coxph.male =
  coxph(
    formula = surv ~ rx + logwbc,
    subset = sex == "male",
    data = anderson)

summary(anderson.coxph.male)
#> Call:
#> coxph(formula = surv ~ rx + logwbc, data = anderson, subset = sex ==
```

```
#>     "male")
#>
#>   n= 20, number of events= 14
#>
#>          coef exp(coef) se(coef)     z Pr(>|z|)
#> rxnew  -1.978     0.138    0.739 -2.68   0.0075 **
#> logwbc  1.743     5.713    0.536  3.25   0.0011 **
#> ---
#> Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
#>
#>        exp(coef) exp(-coef) lower .95 upper .95
#> rxnew      0.138      7.227    0.0325     0.589
#> logwbc     5.713      0.175    1.9991    16.328
#>
#> 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
```

```r
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 '**' 0.01 '*' 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  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?

```r
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     0.189    0.930 -1.79    0.073 .
#> strata(sex)male:logwbc  0.537     1.710    0.735  0.73    0.465
#> ---
#> Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 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
```

```r
anova(
  anderson.coxph.strat.intxn,
  anderson.coxph.strat)
#> # A tibble: 2 x 4
#>   loglik Chisq    Df `Pr(>|Chi|)`
#>    <dbl> <dbl> <int>        <dbl>
#> 1  -53.9 NA       NA       NA
#> 2  -55.7  3.77     2        0.152
```

We don't have enough evidence to tell the difference between these two models.

7.13.5. 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.

7.13.6. Another Modeling Approach

- We used an additive model without interactions and saw that we might need to stratify by sex.
- Instead, we could try to improve the model's functional form - maybe the interaction of treatment and sex is real, and after fitting that we might not need separate hazard functions.
- Either approach may work.

```
anderson.coxph.intxn =
  coxph(
    formula = surv ~ (rx + logwbc) * sex,
    data = anderson)

anderson.coxph.intxn |> summary()
#> Call:
#> coxph(formula = surv ~ (rx + logwbc) * sex, data = anderson)
#>
#>   n= 42, number of events= 30
#>
#>                   coef exp(coef) se(coef)     z Pr(>|z|)
#> rxnew          -0.3748    0.6874   0.5545 -0.68    0.499
#> logwbc          1.0637    2.8971   0.4726  2.25    0.024 *
#> sexmale        -2.8052    0.0605   2.0323 -1.38    0.167
#> 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 '**' 0.01 '*' 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
#> sexmale           0.0605     16.531   0.00113     3.248
#> rxnew:sexmale     0.1132      8.830   0.01899     0.675
#> logwbc:sexmale    3.4223      0.292   0.99539    11.766
#>
#> Concordance= 0.861  (se = 0.036 )
#> Likelihood ratio test= 57  on 5 df,   p=5e-11
#> 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    p
#> rx         0.136  1 0.71
#> logwbc     1.652  1 0.20
#> sex        1.266  1 0.26
#> rx:sex     0.149  1 0.70
#> logwbc:sex 0.102  1 0.75
#> GLOBAL     3.747  5 0.59
```

7.14. Time-varying covariates

(adapted from Klein and Moeschberger (2003), §9.2)

7.14.1. 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    ta    da    tc    dc    tp    dp    z1
#>   <int> <int> <int> <int> <int> <int> <int> <int> <int> <int> <int> <int> <int>
#> 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     1  1496  1496     0     0     0  1496     0   307     1    12     1    26
#> 4     1  1462  1462     0     0     0    70     1    95     1    13     1    17
#> 5     1  1433  1433     0     0     0  1433     0   236     1    12     1    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.

7.14.1.1. 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,

    `patient sex` = 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 |>
      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> <int>         <int>       <int> <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
#> # i 127 more rows
#> # i 6 more variables: `Patient CMV Status` <chr>, `Donor CMV Status` <chr>,
#> #   `Waiting Time to Transplant` <int>, FAB <fct>, hospital <fct>, MTX <lgl>
```

7.14.2. 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.

7.14.3. Analysis in R

- We form a variable `precovery` which is $= 0$ before platelet recovery and is $= 1$ after platelet recovery, if it occurs.

- For each subject where platelet recovery occurs, we set up multiple records (lines in the data frame); for example one from t = 0 to the time of platelet recovery, and one from that time to relapse, recovery, or death.
- We do the same for acute GVHD and chronic GVHD.
- For each record, the covariates are constant.

```
bmt2 = bmt1 |>
  #set up new long-format data set:
  tmerge(bmt1, id = id, tstop = t2) |>

  # the following three steps can be in any order,
  # and will still produce the same result:
  #add aghvd as tdc:
  tmerge(bmt1, id = id, agvhd = tdc(ta)) |>
  #add cghvd as tdc:
  tmerge(bmt1, id = id, cgvhd = tdc(tc)) |>
  #add platelet recovery as tdc:
  tmerge(bmt1, id = id, precovery = tdc(tp))

bmt2 = bmt2 |>
  as_tibble() |>
  mutate(status = as.numeric((tstop == t2) & d3))
# status only = 1 if at end of t2 and not censored
```

Let's see how we've rearranged the first row of the data:

```
bmt1 |>
  dplyr::filter(id == 1) |>
  dplyr::select(id, t1, d1, t2, d2, d3, ta, da, tc, dc, tp, dp)
#> # A tibble: 1 x 12
#>      id    t1    d1    t2    d2    d3    ta    da    tc    dc    tp    dp
#>   <int> <int> <int> <int> <int> <int> <int> <int> <int> <int> <int> <int>
#> 1     1  2081     0  2081     0     0    67     1   121     1    13     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
#>   <int>  <dbl> <int> <int> <int>     <int>  <dbl>
#> 1     1      0    13     0     0         0      0
#> 2     1     13    67     0     0         1      0
#> 3     1     67   121     1     0         1      0
#> 4     1    121  2081     1     1         1      0
```

Note that `status` could have been `1` on the last row, indicating that relapse or death occurred; since it is false, the participant must have exited the study without experiencing relapse or death (i.e., they were censored).

7.14.4. 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.

7.14.5. Model with Time-Fixed Covariates

```r
bmt1 =
  bmt1 |>
  mutate(surv = Surv(t2,d3))

bmt_coxph_TF = coxph(
  formula = surv ~ group + `patient age`*`donor age` + FAB,
  data = bmt1)
summary(bmt_coxph_TF)
#> Call:
#> coxph(formula = surv ~ group + `patient age` * `donor age` +
#>     FAB, data = bmt1)
#>
#>   n= 137, number of events= 83
#>
#>                                  coef exp(coef)  se(coef)     z Pr(>|z|)
#> groupLow Risk AML          -1.090648  0.335999  0.354279 -3.08  0.00208 **
#> groupHigh Risk AML         -0.403905  0.667707  0.362777 -1.11  0.26555
#> `patient age`              -0.081639  0.921605  0.036107 -2.26  0.02376 *
#> `donor age`                -0.084587  0.918892  0.030097 -2.81  0.00495 **
#> FABGrade 4 Or 5 (AML only)  0.837416  2.310388  0.278464  3.01  0.00264 **
#> `patient age`:`donor age`   0.003159  1.003164  0.000951  3.32  0.00089 ***
#> ---
#> Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
#>
#>                            exp(coef) exp(-coef) lower .95 upper .95
#> groupLow Risk AML              0.336      2.976     0.168     0.673
#> groupHigh Risk AML             0.668      1.498     0.328     1.360
#> `patient age`                  0.922      1.085     0.859     0.989
#> `donor age`                    0.919      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
```

```r
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 7.23.: 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, t1, d1,
#> # A tibble: 1 x 13
#>      tp    dp    tc    dc    ta    da FAB     surv    t1    d1    t2    d2    d3
#>   <int> <int> <int> <int> <int> <int> <fct> <Surv> <int> <int> <int> <int> <int>
#> 1    21     1   220     1   418     0 Other    418   418     1   418     0     1
bmt2 |> dplyr::filter(id == 15) |> dplyr::select(id, agvhd, cgvhd, precovery, surv)
#> # A tibble: 3 x 5
#>      id agvhd cgvhd precovery       surv
#>   <int> <int> <int>     <int>     <Surv>
#> 1    15     0     0         0 (  0, 21+]
#> 2    15     0     0         1 ( 21,220+]
#> 3    15     0     1         1 (220,418]
```

7.14.6. 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
#> precovery                  -0.941123  0.390190  0.347861 -2.71   0.0068 **
#> `patient age`:`donor age`   0.002895  1.002899  0.000944  3.07   0.0022 **
#> ---
#> Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 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      1.079     0.873     0.983
#> 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      1.123     0.505     1.569
#> precovery                      0.390      2.563     0.197     0.772
#> `patient age`:`donor age`      1.003      0.997     1.001     1.005
#>
#> Concordance= 0.702  (se = 0.028 )
#> Likelihood ratio test= 40.3  on 9 df,   p=7e-06
#> Wald test            = 42.4  on 9 df,   p=3e-06
#> Score (logrank) test = 47.2  on 9 df,   p=4e-07
```

Platelet recovery is highly significant.

Neither acute GVHD (`agvhd`) nor chronic GVHD (`cgvhd`) has a statistically significant effect here, nor are they significant in models with the other one removed.

```
update(bmt_coxph_TV, .~.-agvhd) |> summary()
#> Call:
#> coxph(formula = surv ~ group + `patient age` + `donor age` +
#>     FAB + cgvhd + precovery + `patient age`:`donor age`, data = bmt2)
#>
#>   n= 341, number of events= 83
#>
#>                                  coef exp(coef)  se(coef)     z Pr(>|z|)
#> groupLow Risk AML          -1.049870  0.349983  0.356727 -2.94   0.0032 **
#> 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 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
#>
#>                            exp(coef) exp(-coef) lower .95 upper .95
#> groupLow Risk AML              0.350      2.857     0.174     0.704
#> groupHigh Risk AML             0.659      1.517     0.322     1.349
#> `patient age`                  0.932      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  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 '**' 0.01 '*' 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
#> `patient age`                  0.929      1.076     0.866     0.997
#> `donor age`                    0.926      1.080     0.873     0.982
#> FABGrade 4 Or 5 (AML only)     2.252      0.444     1.291     3.929
#> agvhd                          1.141      0.877     0.630     2.064
#> precovery                      0.388      2.577     0.196     0.766
#> `patient age`:`donor age`      1.003      0.997     1.001     1.005
#>
#> Concordance= 0.701  (se = 0.027 )
#> Likelihood ratio test= 40.1  on 8 df,   p=3e-06
#> Wald test            = 42.1  on 8 df,   p=1e-06
#> Score (logrank) test = 47.1  on 8 df,   p=1e-07
```

Let's drop them both:

```r
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 **
#> precovery                  -0.983505  0.373998  0.337997 -2.91   0.0036 **
#> `patient age`:`donor age`   0.002872  1.002876  0.000936  3.07   0.0021 **
#> ---
```

```
#> Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
#>
#>                            exp(coef) exp(-coef) lower .95 upper .95
#> groupLow Risk AML              0.356      2.808     0.178     0.712
#> groupHigh Risk AML             0.661      1.513     0.323     1.352
#> `patient age`                  0.931      1.074     0.869     0.999
#> `donor age`                    0.927      1.079     0.874     0.983
#> FABGrade 4 Or 5 (AML only)     2.252      0.444     1.293     3.924
#> precovery                      0.374      2.674     0.193     0.725
#> `patient age`:`donor age`      1.003      0.997     1.001     1.005
#>
#> Concordance= 0.7  (se = 0.027 )
#> Likelihood ratio test= 39.9  on 7 df,   p=1e-06
#> Wald test            = 42.2  on 7 df,   p=5e-07
#> Score (logrank) test = 47.1  on 7 df,   p=5e-08
```

7.15. Recurrent Events

(Adapted from David G. Kleinbaum and Klein (2012), 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.

7.15.1. Bladder Cancer Data Set

The bladder cancer dataset from David G. Kleinbaum and Klein (2012) 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.

7.15.1.1. Data dictionary

Table 7.4.: Variables in the `bladder` dataset

Variable	Definition
`id`	Patient unique ID
`status`	for each time interval: 1 = recurred, 0 = censored
`interval`	1 = first recurrence, etc.

Variable	Definition
`intime`	'`tstop - tstart` (all times in months)
`tstart`	start of interval
`tstop`	end of interval
`tx`	treatment code, 1 = 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.

7.15.1.2. Different intervals for the same patient are correlated.

- Is the effective sample size 47 or 112? This might narrow confidence intervals by as much as a factor of $\sqrt{112/47} = 1.54$
- What happens if I have 5 treatment and 5 control values and want to do a t-test and I then duplicate the 10 values as if the sample size was 20? This falsely narrows confidence intervals by a factor of $\sqrt{2} = 1.41$.

```
bladder =
  paste0(
    "http://web1.sph.emory.edu/dkleinb/allDatasets",
    "/surv2datasets/bladder.dta") |>
  read_dta() |>
  as_tibble()

bladder = bladder[-1,]  #remove subject with 0 observation time
print(bladder)
```

```
bladder =
  bladder |>
  mutate(
    surv =
      Surv(
        time = start,
        time2 = stop,
        event = event,
        type = "counting"))

bladder.cox1 = coxph(
  formula = surv~tx+num+size,
  data = bladder)
```

```
#results with biased variance-covariance matrix:
summary(bladder.cox1)
#> Call:
#> coxph(formula = surv ~ tx + num + size, data = bladder)
#>
#>   n= 190, number of events= 112
#>
#>         coef exp(coef) se(coef)     z Pr(>|z|)
#> tx   -0.4116    0.6626   0.1999 -2.06  0.03947 *
#> num   0.1637    1.1778   0.0478  3.43  0.00061 ***
#> size -0.0411    0.9598   0.0703 -0.58  0.55897
#> ---
#> Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
#>
#>      exp(coef) exp(-coef) lower .95 upper .95
#> tx       0.663      1.509     0.448      0.98
#> num      1.178      0.849     1.073      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  on 3 df,   p=0.001
#> Score (logrank) test = 16.2  on 3 df,   p=0.001
```

> **Note**
>
> The likelihood ratio and score tests assume independence of observations within a cluster. The Wald and robust score tests do not.

7.15.1.3. 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|)
#> tx   -0.4116    0.6626   0.1999    0.2488 -1.65   0.0980 .
#> num   0.1637    1.1778   0.0478    0.0584  2.80   0.0051 **
```

```
#> size -0.0411    0.9598   0.0703    0.0742 -0.55   0.5799
#> ---
#> Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
#>
#>      exp(coef) exp(-coef) lower .95 upper .95
#> tx       0.663      1.509     0.407      1.08
#> num      1.178      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] 1.24449 1.22309 1.05576
```

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 '**' 0.01 '*' 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
#> Wald test            = 10.2  on 2 df,   p=0.006
#> Score (logrank) test = 15.8  on 2 df,   p=4e-04,   Robust = 10.6  p=0.005
#>
#>   (Note: the likelihood ratio and score tests assume independence of
#>      observations within a cluster, the Wald and robust score tests do not).
```

Ways to check PH assumption:

- cloglog
- schoenfeld residuals
- interaction with time

7.16. 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(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' = 6)

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 default
legend_text_size = 9
run_graphs = TRUE
```

8.1. Parametric Survival Models

8.1.1. Exponential Distribution

- The exponential distribution is the basic distribution for survival analysis.

$$
\begin{aligned}
f(t) &= \lambda e^{-\lambda t} \\
\log f(t) &= \log \lambda - \lambda t \\
F(t) &= 1 - e^{-\lambda t} \\
\mathrm{S}(t) &= e^{-\lambda t} \\
\Lambda(t) &= -\log \mathrm{S}(t) \\
&= \lambda t \\
\lambda(t) &= \lambda \\
\mathrm{E}(T) &= \lambda^{-1}
\end{aligned}
$$

8.1.2. Weibull Distribution

Using the Kalbfleisch and Prentice (2002) notation:

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

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

Theorem 8.1. *If T has a Weibull distribution, then:*

- *When $p = 1$, the Weibull distribution simplifies to the exponential distribution*
- *When $p > 1$, the hazard is increasing: $h'(t) > 0$*
- *When $p < 1$, the hazard is decreasing: $h'(t) < 0$*
- *$\log \Lambda(t)$ is a straight line relative to $\log t$: $\log \Lambda(t) = p \log \lambda + p \log t$*

Exercise 8.1. Prove Theorem 8.1.

The Weibull distribution provides more flexibility than the exponential. Figure 8.2 shows 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(expr(lambda)) +
  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:

$$
\begin{aligned}
\eta(\tilde{x}) &= \beta_0 + (\beta_1 x_1 + \cdots + \beta_p x_p) \\
\lambda(t|\tilde{x}) &= \exp\{\eta(\tilde{x})\} \\
\lambda_0 &\stackrel{\text{def}}{=} \lambda(t|\tilde{0}) \\
&= \exp\big\{\eta(\tilde{0})\big\} \\
&= \exp\big\{\beta_0 + (\beta_1 \cdot 0 + \cdots + \beta_p \cdot 0)\big\} \\
&= \exp\{\beta_0 + 0\} \\
&= \exp\{\beta_0\}
\end{aligned}
$$

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:

$$\begin{aligned} h(T=t|X=x) &\stackrel{\text{def}}{=} p(T=t|X=x, T\geq t) \\ &= \lambda(t|X=0)\cdot\exp\{\eta(x)\} \\ &= \lambda(t|X=0)\cdot\theta(x) \\ &= \lambda_0(t)\cdot\theta(x) \end{aligned}$$

and correspondingly,

$$\begin{aligned} \Lambda(t|x) &= \theta(x)\Lambda_0(t) \\ \mathrm{S}(t|x) &= \exp\{-\Lambda(t|x)\} \\ &= \exp\{-\theta(x)\cdot\Lambda_0(t)\} \\ &= (\exp\{-\Lambda_0(t)\})^{\theta(x)} \\ &= (\mathrm{S}_0(t))^{\theta(x)} \end{aligned}$$

An alternative modeling assumption would be

$$\mathrm{S}(t|X=x) = \mathrm{S}_0(t\cdot\theta(x))$$

where $\theta(x)=\exp\{\eta(x)\}$, $\eta(x)=\beta_1 x_1+\cdots+\beta_p x_p$, and $\mathrm{S}_0(t)=\mathrm{P}(T\geq t|X=0)$ is the base survival function.

Then

$$\begin{aligned} \mathrm{E}[T|X=x] &= \int_{t=0}^{\infty}\mathrm{S}(t|x)dt \\ &= \int_{t=0}^{\infty}\mathrm{S}_0(t\cdot\theta(x))dt \\ &= \int_{u=0}^{\infty}\mathrm{S}_0(u)du\cdot\theta(x)^{-1} \\ &= \theta(x)^{-1}\cdot\int_{u=0}^{\infty}\mathrm{S}_0(u)du \\ &= \theta(x)^{-1}\cdot\mathrm{E}[T|X=0] \end{aligned}$$

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:

$$\begin{aligned} \Lambda(t|x) &= \Lambda_0(\theta(x)\cdot t) \\ \lambda(t|x) &= \theta(x)\cdot\lambda_0(\theta(x)\cdot t) \end{aligned}$$

If the base distribution is exponential with parameter λ then

$$\begin{aligned} \mathrm{S}(t|x) &= \exp\{-\lambda\cdot t\theta(x)\} \\ &= [\exp\{-\lambda t\}]^{\theta(x)} \end{aligned}$$

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

$$\begin{aligned} Y &= \alpha - \eta + W \\ \alpha &= -\log \lambda \end{aligned}$$

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

$$\begin{aligned} \lambda(t) &= \lambda p(\lambda t)^{p-1} \\ \mathrm{S}(t) &= e^{-(\lambda t)^p} \end{aligned}$$

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

$$\lambda(t) = \lambda p(\lambda t)^{p-1}\theta_i$$

A distribution with $\lambda(t) = \lambda p(\lambda t)^{p-1}\theta_i$ is a Weibull distribution with parameters $\lambda^* = \lambda\theta_i^{1/p}$ and p so the survival function is

$$\begin{aligned} S^*(t) &= e^{-(\lambda^* t)^p} \\ &= e^{-(\lambda\theta^{1/p} t)^p} \\ &= \mathrm{S}(t\theta^{1/p}) \end{aligned}$$

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

$$\begin{aligned} Y &= \alpha - \sigma\eta + \sigma W \\ \alpha &= -\log \lambda \\ \sigma &= 1/p \end{aligned}$$

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|)
#> rxstandard 1.572     4.817    0.412 3.81  0.00014 ***
#> ---
#> Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
#>
#>            exp(coef) exp(-coef) lower .95 upper .95
#> rxstandard      4.82      0.208      2.15      10.8
#>
#> Concordance= 0.69  (se = 0.041 )
#> Likelihood ratio test= 16.4  on 1 df,   p=5e-05
#> Wald test            = 14.5  on 1 df,   p=1e-04
#> Score (logrank) test = 17.2  on 1 df,   p=3e-05
```

8.1.5.2. Weibull parametric model

```
anderson.weib <- survreg(
  formula = surv ~ rx,
  data = anderson,
  dist = "weibull")
summary(anderson.weib)
#>
#> 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(
  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

9. Summary of Regression Modeling Concepts

9.1. We use different probability models for different data types

- Binary outcomes: Bernoulli models
- Event rate outcomes: Poisson/Negative binomial models
- Time-to-event outcomes: Survival models
- Catch-all: Gaussian models

9.2. We use different link functions to connect these models with covariates

- Bernoulli models: logit link
- Count models: log link + offset
- Survival models: log link
- Gaussian models: identity link

Figure 9.1 sketches how the various models we have studied have analogous structures. To do: convert this sketch into a nicely formatted figure.

Figure 9.1.: Parallel Model Structures

9.3. We use maximum likelihood estimation to fit models to data

- likelihood
- log-likelihood
- score function
- hessian

9.4. We use asymptotic normality of MLEs to quantify uncertainty about models

- observed information matrix
- expected information matrix
- standard error
- confidence intervals
- p-values

9.5. We use (log) likelihood ratios to compare models

Sometimes we adjust these comparisons for model size (AIC, BIC)

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A. Overview of Appendices

These appendices contain information that I consider to be important prerequisites for the main content of this course. I will review *some* of this content in class, but not all of it; there simply isn't enough time to cover it all, and it should be review from your earlier statistics courses. The appendices are also not an exhaustive list of the assumed prerequisites.

Please test yourself on this material; try to write down the definitions from memory, try to solve the proofs for yourself before looking the provided versions, and try to implement the programming solutions before looking at the provided code.

If you find that don't have all of the definitions and results in these appendices memorized yet, now is the time to make it happen.

A.1. Rote memorization is sometimes necessary

For much of my K-12 education, I tried to avoid spending time on rote memorization. Instead, I memorized concepts passively, by repeatedly looking up and applying definitions as I solved problems. I still think that is the most pleasant way to learn, but when I started taking college-level quantitative courses, I found that passive memorization was no longer sufficiently reliable. Especially in the 10-week quarter system, there isn't enough time for new concepts to settle in naturally before we need to use those concepts and construct higher-level concepts on top of them. So, if you are missing any of the concepts in these appendices, please lock them in ASAP. You will need them.

B. Mathematics

> Math is not just a way of calculating numerical answers; it is a way of thinking, using clear definitions for concepts and rigorous logic to organize our thoughts and back up our assertions.

Cheng (2025)

These lecture notes use:

- algebra
- precalculus
- univariate calculus
- linear algebra
- vector calculus

Some key results are listed here.

B.1. Elementary Algebra

Mastery of Elementary Algebra[1] (a.k.a. "College Algebra") is a prerequisite for calculus, which is a prerequisite for Epi 202 and Epi 203, which are prerequisites for this course (Epi 204). Nevertheless, each year, some Epi 204 students are still uncomfortable with algebraic manipulations of mathematical formulas. Therefore, I include this section as a quick reference.

B.1.1. Equalities

Theorem B.1 (Equalities are transitive)**.** *If $a = b$ and $b = c$, then $a = c$*

Theorem B.2 (Substituting equivalent expressions)**.** *If $a = b$, then for any function $f(x)$, $f(a) = f(b)$*

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[1] https://en.wikipedia.org/wiki/Elementary_algebra

B.1.2. Inequalities

Theorem B.3. *If $a < b$, then $a + c < b + c$*

Theorem B.4 (negating both sides of an inequality)**.** *If $a < b$, then: $-a > -b$*

Theorem B.5. *If $a < b$ and $c \geq 0$, then $ca < cb$.*

Theorem B.6.

$$-a = (-1) * a$$

B.1.3. Sums

Theorem B.7 (adding zero changes nothing)**.**

$$a + 0 = a$$

Theorem B.8 (Sums are symmetric)**.**

$$a + b = b + a$$

Theorem B.9 (Sums are associative)**.**

When summing three or more terms, the order in which you sum them does not matter:

$$(a + b) + c = a + (b + c)$$

B.1.4. Products

Theorem B.10 (Multiplying by 1 changes nothing)**.**

$$a \times 1 = a$$

Theorem B.11 (Products are symmetric)**.**

$$a \times b = b \times a$$

Theorem B.12 (Products are associative)**.**

$$(a \times b) \times c = a \times (b \times c)$$

B.1.5. Division

Theorem B.13 (Division can be written as a product)**.**

$$\frac{a}{b} = a \times \frac{1}{b}$$

B.1.6. Sums and products together

Theorem B.14 (Multiplication is distributive)**.**

$$a(b + c) = ab + ac$$

B.1.7. Quotients

Definition B.1 (Quotients, fractions, rates)**.**

A **quotient**, **fraction**, or **rate** is a division of one quantity by another:

$$\frac{a}{b}$$

In epidemiology, rates typically have a quantity involving time or population in the denominator.

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

Definition B.2 (Ratios)**.** A **ratio** is a quotient in which the numerator and denominator are measured using the same unit scales.

c.f. https://en.wikipedia.org/wiki/Ratio

Definition B.3 (Proportion)**.** In statistics, a "proportion" typically means a ratio where the numerator represents a subset of the denominator.

See https://en.wikipedia.org/wiki/Population_proportion.

See also https://en.wikipedia.org/wiki/Proportion_(mathematics) for other meanings.

Definition B.4 (Proportional)**.** Two functions $f(x)$ and $g(x)$ are **proportional** if their ratio $\frac{f(x)}{g(x)}$ does not depend on x. (c.f. https://en.wikipedia.org/wiki/Proportionality_(mathematics))

Additional reference for elementary algebra: https://en.wikipedia.org/wiki/Population_proportion#Mathematical_definition

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B.2. Exponentials and Logarithms

Theorem B.15 (logarithm of a product is the sum of the logs of the factors)**.**

$$\log a \cdot b = \log a + \log b$$

Corollary B.1 (logarithm of a quotient)**.**

The logarithm of a quotient is equal to the difference of the logs of the factors:

$$\log \frac{a}{b} = \log a - \log b$$

Theorem B.16 (logarithm of an exponential function)**.**

$$log\{a^b\} = b \cdot log\{a\}$$

Theorem B.17 (exponential of a sum)**.**

The exponential of a sum is equal to the product of the exponentials of the addends:

$$exp\{a + b\} = exp\{a\} \cdot exp\{b\}$$

Corollary B.2 (exponential of a difference)**.**

The exponential of a difference is equal to the quotient of the exponentials of the addends:

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

Theorem B.18 (exponential of a product)**.**

$$a^{bc} = (a^b)^c = (a^c)^b$$

Corollary B.3 (natural exponential of a product)**.**

$$exp\{ab\} = (exp\{a\})^b = (exp\{b\})^a$$

Exercise B.1. For $a \geq 0,\ b, c \in \mathbb{R}$, When does $(a^b)^c = a^{(b^c)}$?

Solution B.1. Short answer: rarely (that's all you need to know for this course).

Long answer:

If $(a^b)^c = a^{(b^c)}$, then since $(a^b)^c = a^{bc}$, we have:

$$a^{bc} = a^{(b^c)}$$

$$\log\{a^{bc}\} = \log\{a^{(b^c)}\}$$

$$bc \cdot \log\{a\} = b^c \cdot \log\{a\} \tag{B.1}$$

Equation B.1 holds in each of the following cases:

1. $bc = b^c$ (see Exercise B.2).
2. $a = 1$ (i.e., $\log\{a\} = 0$).
3. $a = 0$ (i.e., $\log\{a\} = -\infty$) *and* $\text{sign}\{bc\} = \text{sign}\{b^c\}$.

In particular, when $a = 0$ and $c = 0$, $bc = 0$ and $b^c = 1$ (for any $b \in \mathbb{R}$), so $\text{sign}\{bc\} \neq \text{sign}\{b^c\}$, and $(a^b)^c \neq a^{(b^c)}$:

$$\begin{aligned}(a^b)^c &= (0^b)^0 \\ &= 1\end{aligned}$$

$$\begin{aligned}a^{(b^c)} &= 0^{(b^0)} \\ &= 0^1 \\ &= 0\end{aligned}$$

Exercise B.2. For $b, c \in \mathbb{R}$, when does $b^c = bc$?

Solution B.2. $bc = b^c$ in each of the following cases:

1. $c = 1$.
2. $b = 0$ and $c > 0$.
3. $b = \exp\left\{\frac{\log c}{c-1}\right\}$ (for $c \geq 0$).

See the red contours in Figure B.2 for a visualization.

```r
`b*c_f` <- function(b, c) b*c
`b^c_f` <- function(b, c) b^c
values_b <- seq(0, 5, by = .01)
values_c <- seq(-.5, 3, by = .01)

`b*c` <- outer(values_b, values_c, `b*c_f`)
`b^c` <- outer(values_b, values_c, `b^c_f`)
`b^c`[is.infinite(`b^c`)] = NA

opacity <- .3
z_min <- min(`b*c`, `b^c`, na.rm = TRUE)
z_max <- 5
plotly::plot_ly(
  x = ~values_b,
  y = ~values_c
) |>
  plotly::add_surface(
    z = ~ t(`b*c`),
    contours = list(
      z = list(
        show = TRUE,
        start = -1,
        end = 1,
        size = .1
      )
    ),
    name = "b*c",
    showscale = FALSE,
    opacity = opacity,
    colorscale = list(c(0, 1), c("green", "green"))
  ) |>
  plotly::add_surface(
    opacity = opacity,
    colorscale = list(c(0, 1), c("red", "red")),
    z = ~ t(`b^c`),
    contours = list(
      z = list(
        show = TRUE,
        start = z_min,
        end = z_max,
        size = .2
      )
    ),
    showscale = FALSE,
    name = "b^c"
  ) |>
  plotly::layout(
    scene = list(
      xaxis = list(
        # type = "log",
        title = "b"
      ),
      yaxis = list(
        # type = "log",
        title = "c"
```

```r
`b^c - b*c_f` <- function(b, c) `b^c_f`(b,c) - `b*c_f`(b,c)

mat1 <- outer(values_b, values_c, `b^c - b*c_f`)
mat1[is.infinite(mat1)] = NA

opacity <- .3
plotly::plot_ly(
  x = ~values_b,
  y = ~values_c
) |>
  plotly::add_surface(
    z = ~ t(mat1),
    contours = list(
      z = list(
        show = TRUE,
        start = 0,
        end = 1,
        size = 1,
        color = "red"
      )
    ),
    name = "b^c - b*c",
    showscale = TRUE,
    opacity = opacity
  ) |>
  plotly::layout(
    scene = list(
      xaxis = list(
        # type = "log",
        title = "b"
      ),
      yaxis = list(
        # type = "log",
        title = "c"
      ),
      zaxis = list(
        title = "outcome"
      ),
      camera = list(eye = list(x = -1.25, y = -1.25, z = 0.5)),
      aspectratio = list(x = .9, y = .8, z = 0.7)
    )
  )
```

Theorem B.19 (exp{} and log{} are mutual inverses)**.**

$$exp\{log\{a\}\} = log\{exp\{a\}\} = a$$

B.3. Derivatives

Theorem B.20 (Constant rule)**.**

$$\frac{\partial}{\partial x}c = 0$$

Theorem B.21 (Power rule)**.** *If a is constant with respect to x, then:*

$$\frac{\partial}{\partial x}ay = a\frac{\partial x}{\partial y}$$

Theorem B.22 (Power rule)**.**

$$\frac{\partial}{\partial x}x^q = qx^{q-1}$$

Theorem B.23 (Derivative of natural logarithm)**.**

$$log'\{x\} = \frac{1}{x} = x^{-1}$$

Theorem B.24 (derivative of exponential)**.**

$$exp'\{x\} = exp\{x\}$$

Theorem B.25 (Product rule)**.**

$$(ab)' = ab' + ba'$$

Theorem B.26 (Quotient rule)**.**

$$(a/b)' = a'/b - (a/b^2)b'$$

Theorem B.27 (Chain rule)**.**

$$\begin{aligned}\frac{\partial a}{\partial c} &= \frac{\partial a}{\partial b}\frac{\partial b}{\partial c} \\ &= \frac{\partial b}{\partial c}\frac{\partial a}{\partial b}\end{aligned}$$

or in Euler/Lagrange notation[2]*:*

$$(f(g(x)))' = g'(x)f'(g(x))$$

Corollary B.4 (Chain rule for logarithms)**.**

$$\frac{\partial}{\partial x}\log f(x) = \frac{f'(x)}{f(x)}$$

Proof. Apply Theorem B.27 and Theorem B.23. □

B.4. Linear Algebra

Definition B.5 (Dot product/linear combination/inner product)**.** For any two real-valued vectors $\tilde{x} = (x_1, \dots, x_n)$ and $\tilde{y} = (y_1, \dots, y_n)$, the **dot-product**, **linear combination**, or **inner product** of $\tilde{x}$ and $\tilde{y}$ is:

$$\tilde{x} \cdot \tilde{y} = \tilde{x}^\top \tilde{y} \stackrel{\text{def}}{=} \sum_{i=1}^{n} x_i y_i$$

Note

See also the definitions in

- Dobson and Barnett (2018), §1.3 (equation 1.1, page 7)
- Kaplan (2022), here[a].
- wikipedia[b]

"Linear combination" can also refer to weighted sums of vectors, or in other words matrix-vector multiplication.
The dot-product has a different generalization for two matrices; see wikipedia[c] for more.

[a] https://www.mosaic-web.org/MOSAIC-Calculus/Textbook/Linear-combinations/28-Vectors.html#geometry-arithmetic
[b] https://en.wikipedia.org/wiki/Linear_combination
[c] https://en.wikipedia.org/wiki/Dot_product#Dyadics_and_matrices

[2] https://en.wikipedia.org/wiki/Notation_for_differentiation#Lagrange's_notation

---

Theorem B.28 (Dot product is symmetric)**.** *The dot product is symmetric:*

$$\tilde{x} \cdot \tilde{y} = \tilde{y} \cdot \tilde{x}$$

Proof. Apply:

- Definition B.5
- symmetry of scalar multiplication
- Definition B.5 again

□

B.5. Vector Calculus

(adapted from Fieller (2016), §7.2[3])

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

$$\tilde{x} = \begin{bmatrix} x_1 \\ x_2 \\ \vdots \\ x_p \end{bmatrix}$$

$$\tilde{\beta} = \begin{bmatrix} \beta_1 \\ \beta_2 \\ \vdots \\ \beta_p \end{bmatrix}$$

Definition B.6 (Transpose)**.** The transpose of a row vector is the column vector with the same sequence of entries:

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

Example B.1 (Dot product as matrix multiplication)**.**

$$\begin{aligned} \tilde{x} \cdot \tilde{\beta} &= \tilde{x}^\top \tilde{\beta} \\ &= [x_1, x_2, ..., x_p] \begin{bmatrix} \beta_1 \\ \beta_2 \\ \vdots \\ \beta_p \end{bmatrix} \\ &= x_1\beta_1 + x_2\beta_2 + ... + x_p\beta_p \end{aligned}$$

[3] https://www.taylorfrancis.com/chapters/mono/10.1201/9781315370200-7/vector-matrix-calculus-nick-fieller?context=ubx&refId=c310b723-786a-4f33-ae56-720a6cccd3a1

Theorem B.29 (Transpose of a sum)**.**

$$(\tilde{x} + \tilde{y})^\top = \tilde{x}^\top + \tilde{y}^\top$$

Definition B.7 (Vector derivative)**.** If $f(\tilde{\beta})$ is a function that takes a vector $\tilde{\beta}$ as input, such as $f(\tilde{\beta}) = x'\tilde{\beta}$, then:

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

Definition B.8 (Row-vector derivative)**.** If $f(\tilde{\beta})$ is a function that takes a vector $\tilde{\beta}$ as input, such as $f(\tilde{\beta}) = x'\tilde{\beta}$, then:

$$\frac{\partial}{\partial \tilde{\beta}^\top} f(\tilde{\beta}) = \begin{bmatrix} \frac{\partial}{\partial \beta_1} f(\tilde{\beta}) & \frac{\partial}{\partial \beta_2} f(\tilde{\beta}) & \cdots & \frac{\partial}{\partial \beta_p} f(\tilde{\beta}) \end{bmatrix}$$

Theorem B.30 (Row and column derivatives are transposes)**.**

$$\frac{\partial}{\partial \tilde{\beta}^\top} f(\tilde{\beta}) = \left(\frac{\partial}{\partial \tilde{\beta}} f(\tilde{\beta}) \right)^\top$$

$$\frac{\partial}{\partial \tilde{\beta}} f(\tilde{\beta}) = \left(\frac{\partial}{\partial \tilde{\beta}^\top} f(\tilde{\beta}) \right)^\top$$

Theorem B.31 (Derivative of a dot product)**.**

$$\frac{\partial}{\partial \tilde{\beta}} \tilde{x} \cdot \tilde{\beta} = \frac{\partial}{\partial \tilde{\beta}} \tilde{\beta} \cdot \tilde{x} = \tilde{x}$$

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

Proof.

$$\begin{aligned}\frac{\partial}{\partial\beta}(x^\top\beta) &= \begin{bmatrix}\frac{\partial}{\partial\beta_1}(x_1\beta_1 + x_2\beta_2 + ... + x_p\beta_p)\\ \frac{\partial}{\partial\beta_2}(x_1\beta_1 + x_2\beta_2 + ... + x_p\beta_p)\\ \vdots \\ \frac{\partial}{\partial\beta_p}(x_1\beta_1 + x_2\beta_2 + ... + x_p\beta_p)\end{bmatrix}\\ &= \begin{bmatrix}x_1\\ x_2\\ \vdots\\ x_p\end{bmatrix}\\ &= \tilde{x}\end{aligned}$$

□

Definition B.9 (Quadratic form)**.** A **quadratic form** is a mathematical expression with the structure

$$\tilde{x}^\top \mathbf{S}\tilde{x}$$

where $\tilde{x}$ is a vector and $\mathbf{S}$ is a matrix with compatible dimensions for vector-matrix multiplication.

Quadratic forms occur frequently in regression models. They are the matrix-vector generalizations of the scalar quadratic form $cx^2 = xcx$.

Theorem B.32 (Derivative of a quadratic form)**.** *If S is a $p \times p$ matrix that is constant with respect to β, then:*

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

This is like taking the derivative of cx^2 with respect to x in non-vector calculus.

Corollary B.5 (Derivative of a simple quadratic form)**.**

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

This is like taking the derivative of x^2.

Theorem B.33 (Vector chain rule)**.**

$$\frac{\partial z}{\partial \tilde{x}} = \frac{\partial y}{\partial \tilde{x}} \frac{\partial z}{\partial y}$$

or in Euler/Lagrange notation:

$$(f(g(\tilde{x})))' = \tilde{g}'(\tilde{x}) f(g(\tilde{x}))$$

See https://quickfem.com/finite-element-analysis/, specifically https://quickfem.com/wp-content/uploads/IFEM.AppF_.pdf

See also https://en.wikipedia.org/wiki/Gradient#Relationship_with_Fr%C3%A9chet_derivative

This chain rule is like the univariate chain rule (Theorem B.27), but the order matters now. The version presented here is for the gradient[4] (column vector); the total derivative[5] (row vector) would be the transpose of the gradient[6].

Corollary B.6 (Vector chain rule for quadratic forms)**.**

$$\frac{\partial}{\partial \tilde{\beta}} \left(\tilde{\varepsilon}(\tilde{\beta}) \cdot \tilde{\varepsilon}(\tilde{\beta}) \right) = \left(\frac{\partial}{\partial \tilde{\beta}} \tilde{\varepsilon}(\tilde{\beta}) \right) \left(2\tilde{\varepsilon}(\tilde{\beta}) \right)$$

B.6. Additional resources

B.6.1. Calculus

- Kaplan (2022)
- Khuri (2003)
- Banner (2007)
- Miller (2016)
  - http://www.youtube.com/watch?v=xYzQL0TUtBA
  - http://www.youtube.com/watch?v=Ps2SBo_WjoE

B.6.2. Linear Algebra and Vector Calculus

- Fieller (2016)
- Banerjee and Roy (2014)
- Searle and Khuri (2017)

[4] https://en.wikipedia.org/wiki/Gradient
[5] https://en.wikipedia.org/wiki/Total_derivative
[6] https://en.wikipedia.org/wiki/Gradient#Relationship_with_total_derivative

B.6.3. Numerical Analysis

- Hua Zhou[7]'s lecture notes for "UCLA Biostat 216 - Mathematical Methods for Biostatistics" (2023 Fall)[8]

B.6.4. Real Analysis

- Grinberg (2017)

[7] https://hua-zhou.github.io/
[8] https://ucla-biostat-216.github.io/2023fall/schedule/schedule.html

C. Probability

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(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' = 6)

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 default
legend_text_size = 9
run_graphs = TRUE
```

Most of the content in this chapter should be review from UC Davis Epi 202.

C.1. Core properties of probabilities

C.1.1. Defining probabilities

Definition C.1 (Probability measure)**.** A **probability measure**, often denoted Pr() or P(), is a function whose domain is a σ-algebra[1] of possible outcomes, $\mathcal{S}$, and which satisfies the following properties:

1. For any statistical event $A \in \mathcal{S}$, $\Pr(A) \geq 0$.
2. The probability of the union of all outcomes ($\Omega \stackrel{\text{def}}{=} \cup \mathcal{S}$) is 1:

$$\Pr(\Omega) = 1$$

3. The probability of the union of disjoint events, $A_1 \cup A_2 : A_1 \cap A_2 = \emptyset$, is equal to the sum of their probabilities:

$$\Pr(A_1 \cup A_2) = \Pr(A_1) + \Pr(A_2)$$

Theorem C.1. *If A and B are statistical events and $A \subseteq B$, then* $\Pr(A \cap B) = \Pr(A)$.

Proof. Left to the reader for now. □

---

[1] https://en.wikipedia.org/wiki/%CE%A3-algebra

Theorem C.2.

$$\Pr(A) + \Pr(\neg A) = 1$$

Proof. By properties 2 and 3 of Definition C.1. □

Corollary C.1.

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

Proof. By Theorem C.2 and algebra. □

Corollary C.2. *If the probability of an outcome A is $\Pr(A) = \pi$, then the probability that A does not occur is:*

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

Proof. Using Corollary C.1:

$$\begin{aligned}\Pr(\neg A) &= 1 - \Pr(A) \\ &= 1 - \pi\end{aligned}$$

□

C.2. Random variables

C.2.1. Binary variables

Definition C.2 (binary variable)**.** A **binary variable** is a random variable which has only two possible values in its range.

Exercise C.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)

C.2.2. Count variables

Definition C.3 (Count variable)**.** A **count variable** is a random variable whose possible values are some subset of the non-negative integers; that is, a random variable X such that:

$$\mathcal{R}(X) \in \mathrm{N}$$

Exercise C.2. What are some examples of count variables?

Solution.

- Number of fish in a pond
- Number of cyclones per season
- Seconds of tooth-brushing per session (if rounded)[2]
- Infections per person-year
- Visits to ER per person-month
- Car accidents per 1000 miles driven

Definition C.4 (Exposure magnitude)**.** For many count outcomes, there is some sense of an **exposure magnitude**, such as **population size**, or **duration of observation**, which multiplicatively rescales the expected (mean) count.

Exercise C.3. What are some examples of exposure magnitudes?

---

[2] https://pubmed.ncbi.nlm.nih.gov/35587489/

Solution.

Table C.1.: Examples of exposure units

outcome	exposure units
disease incidence	number of individuals exposed; time at risk
car accidents	miles driven
worksite accidents	person-hours worked
population size	size of habitat

Exposure units are similar to the number of trials in a binomial distribution, but **in non-binomial count outcomes, there can be more than one event per unit of exposure**.

We can use t to represent continuous-valued exposures/observation durations, and n to represent discrete-valued exposures.

Definition C.5 (Event rate)**.**

For a count outcome Y with exposure magnitude t, the **event rate** (denoted λ) is defined as the mean of Y divided by the exposure magnitude. That is:

$$\mu \stackrel{\text{def}}{=} \mathrm{E}[Y|T = t]$$

$$\lambda \stackrel{\text{def}}{=} \frac{\mu}{t} \tag{C.1}$$

Event rate is somewhat analogous to odds in binary outcome models; it typically serves as an intermediate transformation between the mean of the outcome and the linear component of the model. However, in contrast with the odds function, the transformation $\lambda = \mu/t$ is *not* considered part of the Poisson model's link function, and it treats the exposure magnitude covariate differently from the other covariates.

Theorem C.3 (Transformation function from event rate to mean)**.** *For a count variable with mean μ, event rate λ, and exposure magnitude t:*

$$\therefore \mu = \lambda \cdot t \tag{C.2}$$

Solution. Start from definition of event rate and use algebra to solve for μ.

Equation C.2 is analogous to the inverse-odds function for binary variables.

Theorem C.4. *When the exposure magnitude is 0, there is no opportunity for events to occur:*

$$E[Y|T = 0] = 0$$

Proof.

$$\mathrm{E}[Y|T = 0] = \lambda \cdot 0 = 0$$

□

C.2.2.1. Probability distributions for count outcomes

- Poisson distribution
- Negative binomial distribution

C.3. Key probability distributions

Some distributions are typically used for outcome models (Table C.2); other distributions are typically used for test statistics (Table C.3).

Table C.2.: Distributions typically used for outcome models

Distribution	Uses
Bernoulli	Binary outcomes
Binomial	Sums of Bernoulli outcomes
Poisson	unbounded count outcomes
Geometric	Counts of non-events before an event occurs

Distribution	Uses
Negative binomal	Mixtures of Poisson distributions, counts of non-events until a given number of events occurs
Normal (Gaussian)	Continuous outcomes without a more specific distribution
exponential	Time to event outcomes
Gamma	Time to event outcomes
Weibull	Time to event outcomes
Log-normal	Time to event outcomes

Table C.3.: Distributions typically used for test statistics

Distribution	Uses
χ^2	Regression comparisons (asymptotic), contingency table independence tests, goodness-of-fit tests
F	Gaussian model comparisons (exact)
Z (standard normal)	Proportions, means, regression coefficients (asymptotic)
T	Means, regression coefficients in Gaussian outcome models (exact)

C.3.1. The Bernoulli distribution

Definition C.6 (Bernoulli distribution)**.** The **Bernoulli distribution** family for a random variable X is defined as:

$$\begin{aligned}\Pr(X = x) &= 1_{x\in\{0,1\}}\pi^x(1-\pi)^{1-x} \\ &= \begin{cases} \pi, x = 1 \\ 1-\pi, x = 0 \end{cases}\end{aligned}$$

C.3.2. The Poisson distribution

(a) Siméon Denis Poisson

(b) Les Poissons[a]

[a] https://youtu.be/UoJxBEQRLd0?t=12

Figure C.1.: "Les Poissons"

Exercise C.4. Define the Poisson distribution.

Solution C.1.

Definition C.7 (Poisson distribution).

$$\mathrm{P}(Y = y) = \frac{\mu^y e^{-\mu}}{y!}, y \in \mathrm{N} \tag{C.3}$$

(see Figure C.2)

Exercise C.5. What is the range of possible values for a Poisson distribution?

Solution C.2.

$$\mathcal{R}(Y) = \{0, 1, 2, ...\} = \mathrm{N}$$

Theorem C.5 (CDF of Poisson distribution)**.**

$$P(Y \leq y) = e^{-\mu} \sum_{j=0}^{\lfloor y \rfloor} \frac{\mu^j}{j!} \tag{C.4}$$

(see Figure C.3)

```
library(dplyr)
pois_dists <- tibble(
  mu = c(0.5, 1, 2, 5, 10, 20)
) |>
  reframe(
    .by = mu,
    x = 0:30
  ) |>
  mutate(
    `P(X = x)` = dpois(x, lambda = mu),
    `P(X <= x)` = ppois(x, lambda = mu),
    mu = factor(mu)
  )

library(ggplot2)
library(latex2exp)

plot0 <- pois_dists |>
  ggplot(
    aes(
      x = x,
      y = `P(X = x)`,
      fill = mu,
      col = mu
    )
  ) +
  theme(legend.position = "bottom") +
  labs(
```

```
    fill = latex2exp::TeX("$\\mu$"),
    col = latex2exp::TeX("$\\mu$"),
    y = latex2exp::TeX("$\\Pr_{\\mu}(X = x)$")
  )

plot1 <- plot0 +
  geom_segment(yend = 0) +
  facet_wrap(~mu)

print(plot1)
```

Figure C.2.: Poisson PMFs, by mean parameter μ

```
library(ggplot2)

plot2 <-
  plot0 +
  geom_step(alpha = 0.75) +
  aes(y = `P(X <= x)`) +
  labs(y = latex2exp::TeX("$\\Pr_{\\mu}(X \\leq x)$"))

print(plot2)
```

Figure C.3.: Poisson CDFs

Exercise C.6 (Poisson distribution functions)**.** Let $X \sim \text{Pois}(\mu = 3.75)$.

Compute:

- $\text{P}(X = 4|\mu = 3.75)$
- $\text{P}(X \leq 7|\mu = 3.75)$
- $\text{P}(X > 5|\mu = 3.75)$

Solution.

- $\text{P}(X = 4) = 0.19378$
- $\text{P}(X \leq 7) = 0.962379$
- $\text{P}(X > 5) = 0.177117$

Theorem C.6 (Properties of the Poisson distribution)**.** *If $X \sim Pois(\mu)$, then:*

- $E[X] = \mu$
- $Var(X) = \mu$
- $P(X = x) = \frac{\mu}{x} P(X = x - 1)$
- *For* $x < \mu$, $P(X = x) > P(X = x - 1)$
- *For* $x = \mu$, $P(X = x) = P(X = x - 1)$
- *For* $x > \mu$, $P(X = x) < P(X = x - 1)$
- $\arg\max_x P(X = x) = \lfloor \mu \rfloor$

Exercise C.7. Prove Theorem C.6.

Solution.

$$
\begin{aligned}
\mathrm{E}[X] &= \sum_{x=0}^{\infty} x \cdot P(X = x) \\
&= 0 \cdot P(X = 0) + \sum_{x=1}^{\infty} x \cdot P(X = x) \\
&= 0 + \sum_{x=1}^{\infty} x \cdot P(X = x) \\
&= \sum_{x=1}^{\infty} x \cdot P(X = x) \\
&= \sum_{x=1}^{\infty} x \cdot \frac{\lambda^x e^{-\lambda}}{x!} \\
&= \sum_{x=1}^{\infty} x \cdot \frac{\lambda^x e^{-\lambda}}{x \cdot (x-1)!} && \text{[definition of factorial ("!") function]} \\
&= \sum_{x=1}^{\infty} \frac{\lambda^x e^{-\lambda}}{(x-1)!} \\
&= \sum_{x=1}^{\infty} \frac{(\lambda \cdot \lambda^{x-1}) e^{-\lambda}}{(x-1)!} \\
&= \lambda \cdot \sum_{x=1}^{\infty} \frac{(\lambda^{x-1}) e^{-\lambda}}{(x-1)!} \\
&= \lambda \cdot \sum_{y=0}^{\infty} \frac{(\lambda^{y}) e^{-\lambda}}{(y)!} && \text{[substituting } y \stackrel{\text{def}}{=} x - 1\text{]} \\
&= \lambda \cdot 1 && \text{[because PDFs sum to 1]} \\
&= \lambda
\end{aligned}
$$

See also https://statproofbook.github.io/P/poiss-mean.

For the variance, see https://statproofbook.github.io/P/poiss-var.

C.3.2.1. Accounting for exposure

If the exposures/observation durations, denoted $T = t$ or $N = n$, vary between observations, we model:

$$\mu = \lambda \cdot t$$

λ is interpreted as the "expected event rate per unit of exposure"; that is,

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

! 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 $\mathbf{E}[Y|T=0]$**. In other words, this model assumes that if there is no exposure, there can't be any events.

Theorem C.7. *If $\mu = \lambda \cdot t$, then:*

$$\log \mu = \log \lambda + \log t$$

Definition C.8 (Offset)**.** When the linear component of a model involves a term without an unknown coefficient, that term is called an **offset**.

Theorem C.8. *If X and Y are independent Poisson random variables with means μ_X and μ_Y, their sum, $Z = X + Y$, is also a Poisson random variable, with mean $\mu_Z = \mu_X + \mu_Y$.*

Proof. See https://web.stanford.edu/class/archive/cs/cs109/cs109.1206/lectureNotes/LN12_independent_rvs.pdf, Example 3. □

C.3.3. The Negative-Binomial distribution

Definition C.9 (Negative binomial distribution)**.**

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

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

You don't need to memorize or understand this expression.

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.

Theorem C.9. *If $Y \sim NegBin(\mu, \rho)$, then:*

- $E[Y] = \mu$
- $Var(Y) = \mu + \frac{\mu^2}{\rho} > \mu$

C.3.4. Weibull Distribution

$$
\begin{aligned}
p(t) &= \alpha\lambda x^{\alpha-1}\mathrm{e}^{-\lambda x^{\alpha}} \\
\lambda(t) &= \alpha\lambda x^{\alpha-1} \\
\mathrm{S}(t) &= \mathrm{e}^{-\lambda x^{\alpha}} \\
E(T) &= \Gamma(1+1/\alpha)\cdot\lambda^{-1/\alpha}
\end{aligned}
$$

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.

C.4. Characteristics of probability distributions

C.4.1. Probability density function

Definition C.10 (probability density)**.** If X is a continuous random variable, then the **probability density** of X at value x, denoted $f(x)$, $f_X(x)$, $\mathrm{p}(x)$, $\mathrm{p}_X(x)$, or $\mathrm{p}(X = x)$, is defined as the limit of the probability (mass) that X is in an interval around x, divided by the width of that interval, as that width reduces to 0.

$$
f(x) \stackrel{\text{def}}{=} \lim_{\Delta\to 0} \frac{\mathrm{P}(X \in [x, x+\Delta])}{\Delta}
$$

See also Rothman et al. (2021) (Chapter 22, p. 535) and https://en.wikipedia.org/wiki/Probability_density_function#Formal_definition

---

Theorem C.10 (Density function is derivative of CDF)**.** *The density function $f(t)$ or $p(T = t)$ for a random variable T at value t is equal to the derivative of the cumulative probability function $F(t) \stackrel{def}{=} P(T \leq t)$; that is:*

$$
f(t) \stackrel{def}{=} \frac{\partial}{\partial t} F(t)
$$

Theorem C.11 (Density functions integrate to 1)**.** *For any density function $f(x)$,*

$$
\int_{x\in\mathcal{R}(X)} f(x)dx = 1
$$

C.4.2. Hazard function

Definition C.11 (Hazard function, hazard rate, hazard rate function)**.**

The **hazard function**, **hazard rate**, **hazard rate function**, for a random variable T at value t, typically denoted as $\mathrm{h}(t)$ [3] or $\lambda(t)$, [4] is the conditional density of T at t, given $T \geq t$. That is:

$$\lambda(t) \stackrel{\text{def}}{=} \mathrm{p}(T = t | T \geq t)$$

If T represents the time at which an event occurs, then $\lambda(t)$ is the probability that the event occurs at time t, given that it has not occurred prior to time t.

Table C.4.: Probability distribution functions

Name	Symbols	Definition
Probability density function (PDF)	$\mathrm{f}(t), \mathrm{p}(t)$	$\mathrm{p}(T = t)$
Cumulative distribution function (CDF)	$\mathrm{F}(t), \mathrm{P}(t)$	$\mathrm{P}(T \leq t)$
Survival function	$\mathrm{S}(t), \bar{\mathrm{F}}(t)$	$\mathrm{P}(T > t)$
Hazard function	$\lambda(t), \mathrm{h}(t)$	$\mathrm{p}(T = t \mid T \geq t)$
Cumulative hazard function	$\Lambda(t), \mathrm{H}(t)$	$\int_{u=-\infty}^{t} \lambda(u) du$
Log-hazard function	$\eta(t)$	$\log\{\lambda(t)\}$

$$\mathrm{f}(t) \xleftarrow[\mathrm{S}(t)\lambda(t)]{-S'(t)} \mathrm{S}(t) \xleftarrow{\exp\{-\Lambda(t)\}} \Lambda(t) \xleftarrow{\int_{u=0}^{t} \lambda(u) du} \lambda(t) \xleftarrow{\exp\{\eta(t)\}} \eta(t)$$

$$\mathrm{f}(t) \xrightarrow[\int_{u=t}^{\infty} \mathrm{f}(u) du]{\mathrm{f}(t)/\lambda(t)} \mathrm{S}(t) \xrightarrow[-\log \mathrm{S}(t)]{} \Lambda(t) \xrightarrow[\Lambda'(t)]{} \lambda(t) \xrightarrow[\log\{\lambda(t)\}]{} \eta(t)$$

---

[3] for example in Dobson and Barnett (2018), Vittinghoff et al. (2012), Klein and Moeschberger (2003), and David G. Kleinbaum and Klein (2012)

[4] for example, in Rothman et al. (2021) and Kalbfleisch and Prentice (2011)

C.4.3. Expectation

Definition C.12 (Expectation, expected value, population mean)**.** The **expectation**, **expected value**, or **population mean** of a *continuous* random variable X, denoted $\mathrm{E}[X]$, $\mu(X)$, or μ_X, is the weighted mean of X's possible values, weighted by the probability density function of those values:

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

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

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

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

Theorem C.12 (Expectation of the Bernoulli distribution)**.** *The expectation of a Bernoulli random variable with parameter π is:*

$$E[X] = \pi$$

Proof.

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

□

Theorem C.13 (Expectation of time-to-event variables)**.** *If T is a non-negative random variable, then:*

$$\mu(T|\tilde{X} = \tilde{x}) = \int_{t=0}^{\infty} S(t) dt$$

C.4.4. Variance and related characteristics

Definition C.13 (Variance)**.** The variance of a random variable X is the expectation of the squared difference between X and $\mathrm{E}[X]$; that is:

$$\mathrm{Var}(X) \stackrel{\text{def}}{=} \mathrm{E}\big[(X - \mathrm{E}[X])^2\big]$$

Theorem C.14 (Simplified expression for variance)**.**

$$Var(X) = E[X^2] - (E[X])^2$$

Proof. By linearity of expectation, we have:

$$\begin{aligned}
\mathrm{Var}(X) &\stackrel{\text{def}}{=} \mathrm{E}\big[(X - \mathrm{E}[X])^2\big] \\
&= \mathrm{E}\Big[X^2 - 2X\mathrm{E}[X] + (\mathrm{E}[X])^2\Big] \\
&= \mathrm{E}\big[X^2\big] - \mathrm{E}[2X\mathrm{E}[X]] + \mathrm{E}\Big[(\mathrm{E}[X])^2\Big] \\
&= \mathrm{E}\big[X^2\big] - 2\mathrm{E}[X]\mathrm{E}[X] + (\mathrm{E}[X])^2 \\
&= \mathrm{E}\big[X^2\big] - (\mathrm{E}[X])^2
\end{aligned}$$

□

Definition C.14 (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:

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

Definition C.15 (Standard deviation)**.** The standard deviation of a random variable X is the square-root of the variance of X:

$$\mathrm{SD}(X) \stackrel{\text{def}}{=} \sqrt{\mathrm{Var}(X)}$$

Definition C.16 (Covariance)**.** For any two one-dimensional random variables, X, Y:

$$\mathrm{Cov}(X, Y) \stackrel{\text{def}}{=} \mathrm{E}[(X - \mathrm{E}[X])(Y - \mathrm{E}[Y])]$$

Theorem C.15.

$$Cov(X, Y) = E[XY] - E[X]E[Y]$$

Proof. Left to the reader. □

Lemma C.1 (The covariance of a variable with itself is its variance)**.** *For any random variable X:*

$$Cov(X, X) = Var(X)$$

Proof.

$$\begin{aligned}\mathrm{Cov}(X, X) &= E[XX] - E[X]E[X] \\ &= E[X^2] - (E[X])^2 \\ &= \mathrm{Var}(X)\end{aligned}$$

□

Definition C.17 (Variance/covariance of a $p \times 1$ random vector)**.** For a $p \times 1$ dimensional random vector $\tilde{X}$,

$$\begin{aligned}\mathrm{Var}\left(\tilde{X}\right) &\stackrel{\text{def}}{=} \mathrm{Cov}\left(\tilde{X}\right) \\ &\stackrel{\text{def}}{=} \mathrm{E}\left[\left(\tilde{X} - \mathrm{E}\tilde{X}\right)^\top \left(\tilde{X} - \mathrm{E}\tilde{X}\right)\right]\end{aligned}$$

Theorem C.16 (Alternate expression for variance of a random vector)**.**

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

Proof.

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

□

Theorem C.17 (Variance of a linear combination)**.** *For any vector of random variables $\tilde{X} = (X_1, \dots, X_n)$ and corresponding vector of constants $\tilde{a} = (a_1, \dots, a_n)$, the variance of their linear combination is:*

$$\begin{aligned} Var\big(\tilde{a} \cdot \tilde{X}\big) &= Var\left(\sum_{i=1}^{n} a_i X_i\right) \\ &= \tilde{a}^\top Var\big(\tilde{X}\big)\tilde{a} \\ &= \sum_{i=1}^{n}\sum_{j=1}^{n} a_i a_j Cov\big(X_i, X_j\big) \end{aligned}$$

Proof. Left to the reader… □

Corollary C.3. *For any two random variables X and Y and scalars a and b:*

$$Var(aX + bY) = a^2\, Var(X) + b^2\, Var(Y) + 2(a \cdot b)\, Cov(X, Y)$$

Proof. Apply Theorem C.17 with $n = 2$, $X_1 = X$, and $X_2 = Y$.

Or, see https://statproofbook.github.io/P/var-lincomb.html □

Definition C.18 (homoskedastic, heteroskedastic)**.** A random variable Y is **homoskedastic** (with respect to covariates X) if the variance of Y does not vary with X:

$$\mathrm{Var}(Y|X = x) = \sigma^2, \forall x$$

Otherwise it is **heteroskedastic**.

Definition C.19 (Statistical independence)**.** A set of random variables $X_1, \dots, X_n$ are **statistically independent** if their joint probability is equal to the product of their marginal probabilities:

$$\Pr(X_1 = x_1, \dots, X_n = x_n) = \prod_{i=1}^{n} \Pr(X_i = x_i)$$

Tip

The symbol for independence, $\perp\!\!\!\perp$, is essentially just $\prod$ upside-down. So the symbol can remind you of its definition (Definition C.19).

Definition C.20 (Conditional independence)**.** A set of random variables $Y_1, \dots, Y_n$ are **conditionally statistically independent** given a set of covariates $X_1, \dots, X_n$ if the joint probability of the Y_is given the X_is is equal to the product of their marginal probabilities:

$$\Pr(Y_1 = y_1, \dots, Y_n = y_n | X_1 = x_1, \dots, X_n = x_n) = \prod_{i=1}^{n} \Pr(Y_i = y_i | X_i = x_i)$$

Definition C.21 (Identically distributed)**.** A set of random variables $X_1, \dots, X_n$ are **identically distributed** if they have the same range $\mathcal{R}(X)$ and if their marginal distributions $\mathrm{P}(X_1 = x_1), \dots, \mathrm{P}(X_n = x_n)$ are all equal to some shared distribution $\mathrm{P}(X = x)$:

$$\forall i \in \{1 : n\}, \forall x \in \mathcal{R}(X) : \mathrm{P}(X_i = x) = \mathrm{P}(X = x)$$

Definition C.22 (Conditionally identically distributed)**.** A set of random variables $Y_1, \dots, Y_n$ are **conditionally identically distributed** given a set of covariates $X_1, \dots, X_n$ if $Y_1, \dots, Y_n$ have the same range $\mathcal{R}(X)$ and if the distributions $\mathrm{P}(Y_i = y_i | X_i = x_i)$ are all equal to the same distribution $\mathrm{P}(Y = y | X = x)$:

$$\mathrm{P}(Y_i = y | X_i = x) = \mathrm{P}(Y = y | X = x)$$

Definition C.23 (Independent and identically distributed)**.** A set of random variables $X_1, \dots, X_n$ are **independent and identically distributed** (shorthand: "X_i iid") if they are statistically independent and identically distributed.

Definition C.24 (Conditionally independent and identically distributed)**.** A set of random variables $Y_1, \dots, Y_n$ are **conditionally independent and identically distributed** (shorthand: "$Y_i | X_i$ ciid" or just "$Y_i | X_i$ iid") given a set of covariates $X_1, \dots, X_n$ if $Y_1, \dots, Y_n$ are conditionally independent given $X_1, \dots, X_n$ and $Y_1, \dots, Y_n$ are identically distributed given $X_1, \dots, X_n$.

C.5. The Central Limit Theorem

The sum of many independent or nearly-independent random variables with small variances (relative to the number of RVs being summed) produces bell-shaped distributions.

For example, consider the sum of five dice (Figure C.4).

```
library(dplyr)
dist =
  expand.grid(1:6, 1:6, 1:6, 1:6, 1:6) |>
  rowwise() |>
  mutate(total = sum(c_across(everything()))) |>
  ungroup() |>
  count(total) |>
  mutate(`p(X=x)` = n/sum(n))

library(ggplot2)

dist |>
  ggplot() +
  aes(x = total, y = `p(X=x)`) +
  geom_col() +
  xlab("sum of dice (x)") +
  ylab("Probability of outcome, Pr(X=x)") +
  expand_limits(y = 0)
```

Figure C.4.: Distribution of the sum of five dice

In comparison, the outcome of just one die is not bell-shaped (Figure C.5).

```
library(dplyr)
dist =
  expand.grid(1:6) |>
  rowwise() |>
  mutate(total = sum(c_across(everything()))) |>
  ungroup() |>
  count(total) |>
  mutate(`p(X=x)` = n/sum(n))

library(ggplot2)

dist |>
  ggplot() +
  aes(x = total, y = `p(X=x)`) +
  geom_col() +
  xlab("sum of dice (x)") +
  ylab("Probability of outcome, Pr(X=x)") +
  expand_limits(y = 0)
```

Figure C.5.: Distribution of the outcome of one die

What distribution does a single die have?

Answer: discrete uniform on 1:6.

C.6. Additional resources

- Miller (2017)

D. Estimation

D.1. Probabilistic models

Definition D.1 (Scientific models)**. Scientific models** are attempts to describe *physical conditions or changes* that occur in the world and universe around us.

Example D.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.

D.1.1. All models are wrong, some are useful

Box and Draper (1987), p424 (emphasis added):

> …Essentially, all models are wrong, but some are useful. **However, the approximate nature of the model must always be borne in mind.**

see also Dunn and Smyth (2018), §1.8

D.1.2. 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"[1].

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.

[1] https://en.wikipedia.org/wiki/Observer_effect

D.2. Estimands, estimates, and estimators

D.2.1. Estimands

Definition D.2 (Estimand)**.** An **estimand** is an unknown quantity whose value we want to know (Pohl et al. 2021; Lawrance et al. 2020).

Example D.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.

> **Notation for estimands**
>
> Model paramaters and other estimands are often symbolized using lower-case Greek letters: $\alpha, \beta, \gamma, \delta$, etc.

D.2.2. Estimates

Definition D.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 D.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.

D.2.3. Estimators

Definition D.4 (Estimator)**.** An **estimator** is a function $\hat{\theta}(x_1, ...x_n)$ that transforms data $x_1, ...x_n$ into an estimate.

> **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 $\widehat{\ }$ ("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 D.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 D.3 below).

D.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

D.3. Accuracy of estimators

D.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 D.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.

D.3.2. Error

Definition D.6 (Error)**.** The **error** of an estimate $\hat{\theta}$ of a true value θ, often denoted $\varepsilon(\hat{\theta})$, or more completely $\varepsilon(\hat{\theta}, \theta)$, is the difference between the estimate and its estimand θ; that is:

$$\varepsilon(\hat{\theta}) \stackrel{\text{def}}{=} \hat{\theta} - \theta$$

Some frequently-used measures of accuracy include:

D.3.3. Mean squared error

Definition D.7 (Mean squared error)**.** The **mean squared error** of an estimator $\hat{\theta}$, denoted $\mathrm{MSE}\left(\hat{\theta}\right)$, is the expectation of the square of the error[2]:

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

D.3.4. Mean absolute error

Definition D.8 (Mean absolute error)**.** The **mean absolute error** of an estimator is the expectation of the absolute value of the error:

$$\mathrm{MAE}\left(\hat{\theta}\right) \stackrel{\text{def}}{=} \mathrm{E}\left[\left|\varepsilon(\hat{\theta})\right|\right]$$

D.3.5. Bias

Definition D.9 (Bias)**.** The **bias** of an estimator $\hat{\theta}$ for an estimand θ is the expected value of the error:

$$\mathrm{Bias}\left(\hat{\theta}\right) \stackrel{\text{def}}{=} \mathrm{E}\left[\varepsilon(\hat{\theta})\right] \tag{D.1}$$

Theorem D.1 (Bias equals Expectation minus Truth)**.**

$$\mathit{Bias}\left(\hat{\theta}\right) = E\left[\hat{\theta}\right] - \theta$$

Proof.

$$\begin{aligned}
\mathrm{Bias}\left(\hat{\theta}\right) &\stackrel{\text{def}}{=} \mathrm{E}\left[\varepsilon(\hat{\theta})\right] \\
&= \mathrm{E}\left[\hat{\theta} - \theta\right] \\
&= \mathrm{E}\left[\hat{\theta}\right] - \mathrm{E}[\theta] \\
&= \mathrm{E}\left[\hat{\theta}\right] - \theta
\end{aligned}$$

The third equality is by the linearity of expectation. □

[2] https://en.wikipedia.org/wiki/Does_exactly_what_it_says_on_the_tin

---

Theorem D.2 (Mean Squared Error equals Bias Squared plus Variance)**.** *For any one-dimensional estimator $\hat{\theta}$:*

$$MSE\left(\hat{\theta}\right) = \left(Bias\left(\hat{\theta}\right)\right)^2 + Var\left(\hat{\theta}\right) \tag{D.2}$$

Proof. Let's start by expanding each term of the right-hand side:

$$\begin{aligned}\left(\text{Bias}\left(\hat{\theta}\right)\right)^2 &= \left(\text{E}\left[\hat{\theta}\right] - \theta\right)^2 \\ &= \left(\text{E}\left[\hat{\theta}\right]\right)^2 - 2\text{E}\left[\hat{\theta}\right]\theta + \theta^2\end{aligned}$$

$$\text{Var}\left(\hat{\theta}\right) = \text{E}\left[\hat{\theta}^2\right] - \left(\text{E}\left[\hat{\theta}\right]\right)^2$$

Now, add them together and simplify:

$$\begin{aligned}\left(\text{Bias}\left(\hat{\theta}\right)\right)^2 + \text{Var}\left(\hat{\theta}\right) &= \left(\text{E}\left[\hat{\theta}\right]\right)^2 - 2\text{E}\left[\hat{\theta}\right]\theta + \theta^2 + \text{E}\left[\hat{\theta}^2\right] - \left(\text{E}\left[\hat{\theta}\right]\right)^2 \\ &= \text{E}\left[\hat{\theta}^2\right] - 2\text{E}\left[\hat{\theta}\right]\theta + \theta^2\end{aligned}$$

Now let's expand the left-hand side to reach the same expression:

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

$\text{MSE}\left(\hat{\theta}\right)$ and $\left(\text{Bias}\left(\hat{\theta}\right)\right)^2 + \text{Var}\left(\hat{\theta}\right)$ both equal $\text{E}\left[\hat{\theta}^2\right] - 2\text{E}\left[\hat{\theta}\right]\theta + \theta^2$. Equality is transitive, so $\text{MSE}\left(\hat{\theta}\right)$ and $\left(\text{Bias}\left(\hat{\theta}\right)\right)^2 + \text{Var}\left(\hat{\theta}\right)$ are equal to each other:

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

□

D.3.5.1. Unbiased estimators

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

Theorem D.3 (properties of unbiased estimators)**.** *If $\hat{\theta}$ is unbiased, then:*

$$E\left[\hat{\theta}\right] = \theta \tag{D.3}$$

$$MSE\left(\hat{\theta}\right) = Var\left(\hat{\theta}\right) \tag{D.4}$$

Proof. If $\hat{\theta}$ is unbiased, then:

Equation D.3:

$$\begin{aligned}
\text{Bias}\left(\hat{\theta}\right) &= 0 \\
\text{E}\left[\hat{\theta}\right] - \theta &= 0 \\
\text{E}\left[\hat{\theta}\right] &= \theta
\end{aligned}$$

Equation D.4:

$$\begin{aligned}
\text{MSE}\left(\hat{\theta}\right) &\stackrel{\text{def}}{=} \text{E}\left[\left(\varepsilon(\hat{\theta})\right)^2\right] \\
&= \text{E}\left[\left(\hat{\theta} - \theta\right)^2\right] \\
&= \text{E}\left[\left(\hat{\theta} - \text{E}\left[\hat{\theta}\right]\right)^2\right] \\
&\stackrel{\text{def}}{=} \text{Var}\left(\hat{\theta}\right)
\end{aligned}$$

(*Alternative proof of Equation D.4*) We could have started from Theorem D.2 instead:

$$\begin{aligned}
\text{MSE}\left(\hat{\theta}\right) &= \left(\text{Bias}\left(\hat{\theta}\right)\right)^2 + \text{Var}\left(\hat{\theta}\right) \\
&= (0)^2 + \text{Var}\left(\hat{\theta}\right) \\
&= 0 + \text{Var}\left(\hat{\theta}\right) \\
&= \text{Var}\left(\hat{\theta}\right)
\end{aligned}$$

□

D.3.6. Standard error

Definition D.11 (Standard error)**.** The **standard error** of an estimator $\hat{\theta}$ is just the standard deviation of $\hat{\theta}$; that is:

$$\mathrm{SE}\left(\hat{\theta}\right) \stackrel{\text{def}}{=} \mathrm{SD}\left(\hat{\theta}\right)$$

"Standard error" is a confusing concept in a few ways. First of all, it isn't even defined as a characteristic of the error, $\varepsilon(\hat{\theta})$! 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 D.2:

$$\begin{aligned}\mathrm{Var}\left(\hat{\theta}\right) &= \mathrm{Var}\left(\hat{\theta} - \theta\right) \\ &= \mathrm{Var}\left(\varepsilon(\hat{\theta})\right)\end{aligned}$$

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:

$$\mathrm{SE}\left(\hat{\theta}\right) = \mathrm{SD}\left(\varepsilon(\hat{\theta})\right)$$

Corollary D.1 (Standard error squared equals MSE minus squared bias)**.** *standard error is what is left over of MSE after bias is removed:*

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

Proof.

$$\begin{aligned}\mathrm{MSE}\left(\hat{\theta}\right) &= \left(\mathrm{Bias}\left(\hat{\theta}\right)\right)^2 + \mathrm{Var}\left(\hat{\theta}\right) \\ \therefore \mathrm{Var}\left(\hat{\theta}\right) &= \mathrm{MSE}\left(\hat{\theta}\right) - \left(\mathrm{Bias}\left(\hat{\theta}\right)\right)^2 \\ \therefore \left(\mathrm{SE}\left(\hat{\theta}\right)\right)^2 &= \mathrm{MSE}\left(\hat{\theta}\right) - \left(\mathrm{Bias}\left(\hat{\theta}\right)\right)^2\end{aligned}$$

□

Corollary D.2 (For unbiased estimators, SE = RMSE)**.** *If* $E\left[\varepsilon\left(\hat{\theta}\right)\right] = 0$*, then:*

$$SE\left(\hat{\theta}\right) = \sqrt{MSE\left(\hat{\theta}\right)}$$

(this result is equivalent to Equation D.4)

E. Inference

Definition E.1 (Statistical inference)**.** Statistical inference is the process of analyzing data in order to learn about the shape and structure of a probability distribution. [1]

Statistical inference typically consists of two steps:

1. fitting a statistical model to data
2. summarizing our uncertainty about the parameters of the fitted model based on the data (and our prior beliefs).

There are two predominant paradigms for statistical inference:

1. Bayesian inference (Appendix G)
2. Frequentist inference (Appendix F)

E.1. Interpretation of Negative Findings

If an estimation interval includes the null hypothesis, or equivalently if a hypothesis test fails to reject the null hypothesis, that doesn't *necessarily* mean that the null hypothesis is true. Accordingly, we should not write interpretations of results as "the odds (or risks/hazards/means) are not significantly different"; instead, we should write something like "the data does not provide statistically significant EVIDENCE that the odds (or analogous estimands) differ". Statistical significance is a characteristic of evidence, not of the estimands.

P-values do not distinguish between absence of evidence and evidence of absence.

Confidence intervals do: if the confidence interval is narrow and includes the null value, then that confidence interval represents evidence of absence. If a confidence interval includes the null value but also includes substantially non-null values, then that confidence interval represents absence of evidence.

Also, even if we do have statistically significant evidence of a non-null value, the estimated value may not be **substantially different from 0**, depending on what estimand is. For example, we might have statistically significant evidence that a certain exercise prolongs

[1] I adapted this definition from Wikipedia's (Wikipedia contributors 2025).

human lifespans by 20 seconds, but that effect would probably not be substantially different from 0 in practical terms.

Figure E.1 sketches various scenarios for confidence intervals, from office hours. To do: convert this sketch into a nicely formatted figure.

Figure E.1.: Interpretations of various confidence intervals

See also Vittinghoff et al. (2012) §3.7 (p64).

E.2. Confidence intervals

Definition E.2 (margin of error)**.** The **margin of error** (a.k.a. the **radius**) is one-half the width of a confidence interval.

more:

- Anatomy of a confidence interval (text)[2]
- https://www.youtube.com/watch?v=vq1KrE7gU5M

[2] https://wmed.edu/sites/default/files/ANATOMY%20OF%20A%20CONFIDENCE%20INTERVAL%20%28full%29.pdf

F. Introduction to Maximum Likelihood Inference

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(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' = 6)

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 default
legend_text_size = 9
run_graphs = TRUE
```

F.1. Overview of maximum likelihood estimation

F.1.1. The likelihood function

Definition F.1 (Likelihood of a single observation)**.** Let X be a random variable and let x be X's observed data value. Let $\mathrm{p}_\Theta(X = x)$ be a probability model for the distribution of X, with parameter vector Θ.

Then the **likelihood** of parameter value θ, for model $\mathrm{p}_\Theta(X = x)$ and data $X = x$, is simply the probability of the event $X = x$ given $\Theta = \theta$:

$$\mathcal{L}(\theta) \stackrel{\text{def}}{=} \mathrm{P}_\theta(X = x)$$

Definition F.2 (Likelihood of a dataset)**.** Let $\tilde{x} \stackrel{\text{def}}{=} x_1, \dots, x_n$ be a dataset with corresponding random variable $\tilde{X}$. Let $\mathrm{p}_\Theta(\tilde{X})$ be a probability model for the distribution of $\tilde{X}$ with unknown parameter vector Θ.

Then the **likelihood** of parameter value θ, for model $\mathrm{p}_\Theta(X)$ and data $\tilde{X} = \tilde{x}$, is the *joint probability* of $\tilde{X} = \tilde{x}$ given $\Theta = \theta$:

$$\begin{aligned}\mathcal{L}(\theta) &\stackrel{\text{def}}{=} \mathrm{p}(\tilde{X} = \tilde{x} | \Theta = \theta) \\ &= \mathrm{p}(X_1 = x_1, \dots, X_n = x_n | \Theta = \theta)\end{aligned}$$

Notation for the likelihood function

The likelihood function can be written as:

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

All of these notations mean the same thing. The parameter vector θ is often listed first or solely, either to emphasize that we are interested in how this function varies with the parameters, given the data, or possibly to make the likelihood resemble the Bayesian posterior probability $\mathrm{p}(\theta|\tilde{x})$, hinting at the fact that if the prior probability $\mathrm{p}(\theta)$ is uniform over some finite parameter space, the posterior probability is proportional to the likelihood:

$$\begin{aligned}\mathrm{p}(\theta|\tilde{x}) &= \frac{\mathrm{p}(\tilde{x}|\theta)\mathrm{p}(\theta)}{\mathrm{p}(\tilde{x})} \\ &= \frac{\mathcal{L}(\tilde{x}|\theta)\mathrm{p}(\theta)}{\mathrm{p}(\tilde{x})} \\ &= \mathcal{L}(\tilde{x}|\theta)\frac{\mathrm{p}(\theta)}{\mathrm{p}(\tilde{x})}\end{aligned}$$

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 F.1 (Likelihood of an independent sample)**.** *For mutually independent data $X_1, ..., X_n$:*

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

Proof.

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

The second equality is by the definition of statistical independence. □

Definition F.3 (Likelihood components)**.** Given an iid dataset $\tilde{x}$, the **likelihood component** or **likelihood factor** of observation $X_i = x_i$ is the marginal likelihood of $X_i = x_i$:

$$\mathcal{L}_i(\theta) = \mathrm{P}(X_i = x_i)$$

Theorem F.2. *For iid data $\tilde{x} \stackrel{def}{=} x_1, \dots, x_n$, the likelihood of the dataset is equal to the product of the observation-specific likelihood factors:*

$$\mathcal{L}(\theta) = \prod_{i=1}^{n} \mathcal{L}_i(\theta)$$

F.1.2. Binary outcomes models - one group, no covariates

$$\begin{aligned}
&\mathrm{P}(Y = 1) = \pi \\
&\mathrm{P}(Y = 0) = 1 - \pi \\
&\mathrm{P}(Y = y) = \pi^y (1 - \pi)^{1-y}
\end{aligned}$$

Exercise F.1. Let $\tilde{y}$ represent a data set of mutually independent binary outcomes, all with the same event probability π:

$$\begin{aligned}
\tilde{y} &= (y_1, ..., y_n) \\
y_i &\sim_{\perp\!\!\!\perp} \mathrm{Ber}(\pi)
\end{aligned}$$

Write the likelihood of $\tilde{y}$.

Solution F.1. For iid data $\tilde{y} = (y_1, ..., y_n)$:

$$\begin{aligned}
\mathcal{L}(\pi; \tilde{y}) &= \mathrm{P}(Y_1 = y_1, \dots, Y_n = y_n) \\
&= \prod_{i=1}^{n} \mathcal{L}_i(\pi_i) \\
&= \prod_{i=1}^{n} \mathrm{P}(Y_i = y_i) \\
&= \prod_{i=1}^{n} \pi^{y_i} (1 - \pi)^{1-y_i} \\
&= \pi^{\sum_{i=1}^{n} y_i} (1 - \pi)^{n - \sum_{i=1}^{n} y_i} \\
&= \pi^{\tilde{1} \cdot \tilde{y}} (1 - \pi)^{\tilde{1} \cdot (\tilde{1} - \tilde{y})}
\end{aligned}$$

Exercise F.2. Write the log-likelihood of $\tilde{y}$.

Solution F.2.

$$\begin{aligned}
\ell(\pi, \tilde{y}) &= \left(\sum_{i=1}^{n} y_i\right) \log\{\pi\} + \left(n - \sum y_i\right) \log\{1-\pi\} \\
&= \left(\sum_{i=1}^{n} y_i\right) (\log\{\pi\} - \log\{1-\pi\}) + n \cdot \log\{1-\pi\} \\
&= \left(\sum_{i=1}^{n} y_i\right) \log\left\{\frac{\pi}{1-\pi}\right\} + n \cdot \log\{1-\pi\} \\
&= \left(\sum_{i=1}^{n} y_i\right) \operatorname{logit}(\pi) + n \cdot \log\{1-\pi\}
\end{aligned}$$

F.1.3. The maximum likelihood estimate

Definition F.4 (Maximum likelihood estimate)**.** The **maximum likelihood estimate** of a parameter vector Θ, denoted $\hat{\theta}_{\text{ML}}$, is the value of Θ that maximizes the likelihood:

$$\hat{\theta}_{\text{ML}} \stackrel{\text{def}}{=} \arg\max_{\Theta} \mathcal{L}(\Theta) \tag{F.2}$$

F.1.4. 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 ($f''(x) < 0$).

F.1.5. Directly maximizing the likelihood function for independent 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:

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

The derivative of the likelihood of independent data is the derivative of a product. To evaluate this derivative, we will have to perform a massive application of the product rule (Theorem B.25).

F.1.6. The log-likelihood function

It is typically easier to work with the log of the likelihood function:

Definition F.5 (Log-likelihood)**.** The **log-likelihood** of parameter value θ, for model $\mathrm{p}_\Theta(\tilde{X})$ and data $\tilde{X} = \tilde{x}$, is the natural logarithm of the likelihood[1]:

$$\ell \stackrel{\text{def}}{=} \log\{\mathcal{L}(\tilde{x}|\theta)\} \tag{F.4}$$

Theorem F.3. *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 F.4 (Log-likelihood of an independent sample)**.** *For mutually independent data $X_1, ..., X_n$ with shared distribution $p(X = x)$:*

$$\ell(x|\theta) = \sum_{i=1}^n \log p(X = x_i|\theta) \tag{F.5}$$

Proof.

$$\begin{aligned}\ell(x|\theta) &\stackrel{\text{def}}{=} \log \mathcal{L}(\tilde{x}|\theta) \\ &= \log \prod_{i=1}^n \mathrm{p}(X_i = x_i|\theta) \\ &= \sum_{i=1}^n \log p(X = x_i|\theta)\end{aligned}$$

□

For iid data, we will have a much easier time taking the derivative of the log-likelihood:

Theorem F.5 (Derivative of the log-likelihood function for iid data)**.** *For iid data:*

$$\ell'(\theta) = \sum_{i=1}^n \frac{\partial}{\partial\theta} \log p(X = x_i|\theta) \tag{F.6}$$

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

Proof.

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

□

F.1.7. The score function

The first derivative[2] of the log-likelihood, $\ell'(\theta)$, is important enough to have its own name: the *score function*.

Definition F.6 (Score function)**.** The **score function** of a statistical model $\mathrm{p}(\tilde{X} = \tilde{x})$ is the gradient (i.e., first derivative) of the log-likelihood of that model:

$$\ell' \stackrel{\text{def}}{=} \frac{\partial}{\partial\theta}\ell(\tilde{x}|\theta) \tag{F.7}$$

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'. We will use ℓ', both to save U and S for other uses and to avoid introducing unnecessary notation to memorize.

Exercise F.3. Derive the score function for a single Bernoulli random variable X. In other words, differentiate the marginal log-likelihood of a single Bernoulli random variable X with respect to the event probability parameter, π. Simplify as much as possible.

Solution F.3. Starting from Solution F.2:

[2] a.k.a. the gradient[3]

$$
\begin{aligned}
\ell' &\stackrel{\text{def}}{=} \frac{\partial}{\partial \pi}\ell \\
&= \frac{\partial}{\partial \pi}(x\log\{\pi\} + (1-x)\log\{1-\pi\}) \\
&= \frac{\partial}{\partial \pi}x\log\{\pi\} + \frac{\partial}{\partial \pi}(1-x)\log\{1-\pi\} \\
&= x\frac{\partial}{\partial \pi}\log\{\pi\} + (1-x)\frac{\partial}{\partial \pi}\log\{1-\pi\} \\
&= x\frac{1}{\pi} - (1-x)\frac{1}{1-\pi} \\
&= x\frac{1-\pi}{\pi(1-\pi)} - (1-x)\frac{\pi}{\pi(1-\pi)} \\
&= \frac{x(1-\pi)-(1-x)\pi}{\pi(1-\pi)} \\
&= \frac{x - x\pi - \pi + x\pi}{\pi(1-\pi)} \\
&= \frac{x-\pi}{\pi(1-\pi)} \\
&= \frac{x-\mu}{\pi(1-\pi)} \\
&= \frac{\varepsilon}{\mathrm{Var}(X)}
\end{aligned}
$$

Exercise F.4. Derive the score function for a single Poisson random variable X.

Solution F.4. The score function is the first derivative of the log-likelihood:

$$
\begin{aligned}
\ell' &= \frac{\partial}{\partial \lambda}(x\log\lambda - \lambda - \log x!) \\
&= \frac{\partial}{\partial \lambda}x\log\lambda - \frac{\partial}{\partial \lambda}n\lambda - \frac{\partial}{\partial \lambda}\log x! \\
&= x\frac{\partial}{\partial \lambda}\log\lambda - n\frac{\partial}{\partial \lambda}\lambda - \frac{\partial}{\partial \lambda}\log x! \\
&= x\frac{1}{\lambda} - 1 - 0 \\
&= \frac{1}{\lambda}x - 1 \\
&= \frac{x}{\lambda} - \frac{\lambda}{\lambda} \\
&= \frac{x-\lambda}{\lambda} \\
&= \frac{x-\mu}{\lambda} \\
&= \frac{\varepsilon}{\mathrm{Var}(X)}
\end{aligned}
$$

Exercise F.5. Derive the score function for a single Gaussian random variable X, with respect to the mean parameter μ.

Solution F.5. The score function is the first derivative of the log-likelihood:

$$\begin{aligned}
\ell' &\stackrel{\text{def}}{=} \frac{\partial}{\partial\mu}\ell \\
&= \frac{\partial}{\partial\mu}\left(\frac{-1}{2}\left(\log\{2\pi\sigma^2\} + \frac{\varepsilon^2}{\sigma^2}\right)\right) \\
&= \frac{-1}{2}\frac{\partial}{\partial\mu}\left(\log\{2\pi\sigma^2\} + \frac{\varepsilon^2}{\sigma^2}\right) \\
&= \frac{-1}{2}\left(\frac{\partial}{\partial\mu}\log\{2\pi\sigma^2\} + \frac{\partial}{\partial\mu}\frac{\varepsilon^2}{\sigma^2}\right) \\
&= \frac{-1}{2}\left(0 + \frac{\partial}{\partial\mu}\frac{(x-\mu)^2}{\sigma^2}\right) \\
&= \frac{-1}{2}\left(-2\frac{x-\mu}{\sigma^2}\right) \\
&= \frac{x-\mu}{\sigma^2} \\
&= \frac{\varepsilon}{\mathrm{Var}(X)}
\end{aligned}$$

Exercise F.6. Derive the score function for a single exponential random variable X, with respect to the mean parameter μ.

Solution F.6. The score function is the first derivative of the log-likelihood:

$$\begin{aligned}
\ell' &\stackrel{\text{def}}{=} \frac{\partial}{\partial\mu}\ell \\
&= \frac{\partial}{\partial\mu}\left(-\log\{\mu\} - \frac{x}{\mu}\right) \\
&= \frac{\partial}{\partial\mu}(-\log\{\mu\}) - \frac{\partial}{\partial\mu}\frac{x}{\mu} \\
&= -\frac{1}{\mu} + \frac{x}{\mu^2} \\
&= -\frac{\mu}{\mu^2} + \frac{x}{\mu^2} \\
&= \frac{x-\mu}{\mu^2} \\
&= \frac{\varepsilon}{\mathrm{Var}(X)}
\end{aligned}$$

In all four cases above, the score function (with respect to the mean) turned out to be:

$$\ell' = \frac{\varepsilon}{\mathrm{Var}(X)}$$

That is no coincidence. All four of these distributions belong to the exponential family/class of probability distributions[4]. The distributions in the exponential family share many special properties. For more details, see Hogg, Tanis, and Zimmerman (2015), Section 6.7 and Dobson and Barnett (2018), Chapter 3.

F.1.8. Asymptotic distribution of the maximum likelihood estimate

We learned how to quantify our uncertainty about these maximum likelihood estimates; with sufficient sample size, $\hat{\theta}_{\mathrm{ML}}$ has an approximately Gaussian distribution (Newey and McFadden 1994):

Theorem F.6 (Central limit theorem for MLEs)**.**

$$\hat{\theta}_{ML} \dot{\sim} N\Big(\theta, \big[\mathcal{J}(\tilde{\theta})\big]^{-1}\Big) \tag{F.8}$$

Proof. See (Lehmann 1999), Theorem 7.3.2. □

Recall:

Definition F.7 (Observed information matrix)**.** The **observed information matrix**, denoted I, is defined as the negative of the Hessian of the log-likelihood:

$$I \stackrel{\text{def}}{=} -\ell''(\tilde{x}|\tilde{\theta}) \tag{F.9}$$

Definition F.8 (Expected information/Fisher information)**.** The **expected information matrix**, also known as the **Fisher information matrix**, is denoted $\mathcal{J}$ and is defined as the expected value of the observed information matrix:

$$\mathcal{J} \stackrel{\text{def}}{=} \mathrm{E}[I(\tilde{x}|\theta)] \tag{F.10}$$

We can estimate $\mathcal{J}(\theta)$ using either $\mathcal{J}(\hat{\theta}_{\mathrm{ML}})$ or $I(\tilde{x}; \hat{\theta}_{\mathrm{ML}})$.

So we can estimate the standard error of $\hat{\theta}_k$ as:

$$\widehat{\mathrm{SE}}\big(\hat{\theta}_k\big) = \sqrt{\Big[\big(\hat{\mathcal{J}}\big(\hat{\theta}_{\mathrm{ML}}\big)\big)^{-1}\Big]_{kk}}$$

[4] https://en.wikipedia.org/wiki/Exponential_family

F.1.9. 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 $\mathcal{I}(I)$ (`\scriptI` in Unicode, `\mathcal{I}` in LaTeX).

$$\begin{aligned}\mathcal{I} &\stackrel{\text{def}}{=} \mathcal{I}(\theta)\\ &\stackrel{\text{def}}{=} \mathrm{Cov}(\ell'|\theta)\\ &= \mathrm{E}[\ell'\ell'^{\top}] - \mathrm{E}[\ell']\ \mathrm{E}[\ell']^{\top}\end{aligned}$$

The elements of $\mathcal{I}$ are:

$$\begin{aligned}\mathcal{I}_{ij} &\stackrel{\text{def}}{=} \mathrm{Cov}\big(\ell'_i, \ell'_j\big)\\ &= \mathrm{E}[\ell'_i\ell'_j] - \mathrm{E}[\ell'_i]\mathrm{E}[\ell'_j]\end{aligned}$$

Here,

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

And similarly

$$\mathrm{E}[\ell'\ell'^{\top}] \stackrel{\text{def}}{=} \int_{x\in R(x)} \ell'(x,\theta)\ell'(x,\theta)^{\top}\ \mathrm{p}(X=x|\theta)\ dx$$

Note that $\mathrm{E}[\ell']$ and $\mathrm{E}\Big[\ell'\ell'^{\top}\Big]$ 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):

$$\mathrm{E}[\ell'] = 0$$

So

$$\mathcal{I}(\theta) = \mathrm{E}\Big[\ell'\ell'^{\top}\Big]$$

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

$$\mathcal{I} = -\mathrm{E}[\ell''] = \mathrm{E}[-\ell'\ell'^{\top}]$$

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

Definition F.9 (Hessian)**.** The matrix of second derivatives of the log-likelihood function is called the **Hessian matrix (of the log-likelihood function)** [5]:

$$\ell'' \stackrel{\text{def}}{=} \frac{\partial}{\partial \tilde{\theta}} \frac{\partial}{\partial \tilde{\theta}^\top} \ell(\tilde{x}|\tilde{\theta}) \tag{F.11}$$

Theorem F.7 (Elements of the Hessian matrix)**.** *If $\tilde{\theta}$ is a $p \times 1$ vector, then the Hessian is a $p \times p$ matrix, whose ij^{th} entry is:*

$$\ell''_{ij} = \frac{\partial}{\partial \theta_i} \frac{\partial}{\partial \theta_j} \ell(\tilde{X} = \tilde{x}|\tilde{\theta}) \tag{F.12}$$

Theorem F.8 (Hessian = derivative of transposed score)**.**

$$\ell''(\tilde{x}|\tilde{\theta}) = \frac{\partial}{\partial \tilde{\theta}} \Big(\ell'(\tilde{x}|\tilde{\theta}) \Big)^\top$$

F.1.9.1. Observed information

Sometimes, we use $I(\theta; x) \stackrel{\text{def}}{=} -hess$ (note the standard-font "I" here). $I(\theta; x)$ is the observed information, precision, or concentration matrix (Negative Hessian).

> **!** Key point
>
> The asymptotics of MLEs gives us $\hat{\theta}_{ML} \sim N(\theta, \mathfrak{I}^{-1}(\theta))$, approximately, for large sample sizes.

We can estimate $\mathcal{I}^{-1}(\theta)$ by working out $\mathrm{E}[-\ell'']$ or $\mathrm{E}\Big[\ell' \ell'^\top\Big]$ 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)).

[5] named after mathematician Otto Hesse[6]

F.1.10. Quantifying (un)certainty of MLEs

F.1.10.1. Confidence intervals for MLEs

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

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

where z_β the β quantile of the standard Gaussian distribution.

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

(to add)

F.1.10.3. Likelihood ratio tests for MLEs

log(likelihood ratio) tests (c.f. Dobson and Barnett 2018, sec. 5.7):

$$2(\ell - \ell_{\mathrm{H0}}) \sim \chi^2(p-q)$$

See also https://online.stat.psu.edu/stat504/book/export/html/657

F.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).

F.2. Example: Maximum likelihood for Tropical Cyclones in Australia

(Adapted from Dobson and Barnett (2018) §1.6.5)

F.2.1. Data

The `cyclones` dataset in the `dobson` package (Table F.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 F.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.

F.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 F.1.: Number of tropical cyclones during a season from November to April in North-eastern 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 = factor(years, levels = 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 F.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_is are identically distributed.

We can visualize the distribution using a bar plot (Figure F.2).

```
cyclones |>
  ggplot() +
  geom_histogram(aes(x = number)) +
  expand_limits(x = 0) +
  xlab("Number of cyclones") +
  ylab("Count (number of seasons)")
```

Table F.2.: Summary statistics for `cyclones` data

	Overall (N=13)
number	
Mean (SD)	5.54 (2.47)
Median [Min, Max]	6.00 [2.00, 12.0]

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

Table F.2 provides summary statistics.

```
n <- nrow(cyclones)
sumx <- cyclones |>
  pull(number) |>
  sum()
xbar <- cyclones |>
  pull(number) |>
  mean()

cyclones |> table1::table1(x = ~number)
```

F.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 F.7. 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 F.8. Write down the Poisson distribution's probability mass function.

Solution.

$$P(Y = y) = \frac{\lambda^y e^{-\lambda}}{y!} \tag{F.13}$$

F.2.4. Estimating the model parameters using maximum likelihood

Now, we can estimate the parameter λ for this distribution using maximum likelihood estimation.

Exercise F.9 (What is the likelihood?)**.** Write down the likelihood (probability mass function or probability density function) of a single observation x, according to your model.

Solution.

$$\begin{aligned}\mathcal{L}(\lambda; x) &= p(X = x | \Lambda = \lambda) \\ &= \frac{\lambda^x e^{-\lambda}}{x!}\end{aligned}$$

Exercise F.10. Write down the vector of parameters in your model.

Solution. There is only one parameter, λ:

$$\theta = (\lambda)$$

Exercise F.11. 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: $\mathrm{E}[X] = \lambda$
- Population variance: $\mathrm{Var}(X) = \lambda$

Exercise F.12. Write down the likelihood of the full dataset.

Solution.

$$\begin{aligned}
\mathcal{L}(\lambda; \tilde{x}) &= \mathrm{P}(\tilde{X} = \tilde{x}) \\
&= \mathrm{P}(X_1 = x_1, X_2 = x_2, ..., X_{13} = x_{13}) \\
&= \prod_{i=1}^{13} \mathrm{P}(X_i = x_i) \\
&= \prod_{i=1}^{13} \frac{\lambda^{x_i} e^{-\lambda}}{x_i!}
\end{aligned}$$

Exercise F.13. Graph the likelihood as a function of λ.

Solution.

```r
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 F.3.: Likelihood of Dobson cyclone data

Exercise F.14. Write down the log-likelihood of the full dataset.

Solution.

$$
\begin{aligned}
\ell(\lambda; \tilde{x}) &= \log \mathcal{L}(\lambda; \tilde{x}) \\
&= \log \prod_{i=1}^{n} \frac{\lambda^{x_i} \mathrm{e}^{-\lambda}}{x_i!} \\
&= \sum_{i=1}^{n} \log \frac{\lambda^{x_i} \mathrm{e}^{-\lambda}}{x_i!} \\
&= \sum_{i=1}^{n} \log \lambda^{x_i} + \log \mathrm{e}^{-\lambda} - \log x_i! \\
&= \sum_{i=1}^{n} x_i \log \lambda - \lambda - \log x_i! \\
&= \sum_{i=1}^{n} x_i \log \lambda - \sum_{i=1}^{n} \lambda - \sum_{i=1}^{n} \log x_i! \\
&= \sum_{i=1}^{n} x_i \log \lambda - n\lambda - \sum_{i=1}^{n} \log x_i!
\end{aligned}
$$

Exercise F.15. 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 F.4.: log-likelihood of Dobson cyclone data

F.2.4.1. The score function

Exercise F.16. Derive the score function for the dataset.

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

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

Exercise F.17. 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 F.5.: score function of Dobson cyclone data

F.2.4.2. The Hessian matrix

Exercise F.18. Derive the Hessian matrix.

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

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

Exercise F.19. 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 F.6.: Hessian function of Dobson cyclone data

Exercise F.20. Write the score equation (estimating equation).

Solution.

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

F.2.5. Finding the MLE analytically

In this case, we can find the MLE of λ by solving the score equation for λ analytically (using algebra):

Exercise F.21. Solve the estimating equation for λ:

Solution.

$$\begin{aligned}
0 &= \frac{1}{\lambda}\sum_{i=1}^{n} x_i - n \\
n &= \frac{1}{\lambda}\sum_{i=1}^{n} x_i \\
n\lambda &= \sum_{i=1}^{n} x_i \\
\lambda &= \frac{1}{n}\sum_{i=1}^{n} x_i \\
&= \bar{x}
\end{aligned}$$

Let's call this solution of the estimating equation $\tilde{\lambda}$ for now:

$$\tilde{\lambda} \stackrel{\text{def}}{=} \bar{x}$$

Exercise F.22. Confirm that the Hessian $\ell''(\lambda; \tilde{x})$ is negative when evaluated at $\tilde{\lambda}$.

Solution.

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

Exercise F.23. Draw conclusions about 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 $\mathcal{L}(\lambda; \tilde{x})$:

```
mle <- mean(cyclones$number)
```

$$\hat{\lambda}_{\text{ML}} = \bar{x} = 5.538462$$

Exercise F.24. 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 F.7.: log-likelihood of Dobson cyclone data with MLE

F.2.5.1. 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 F.8.: Observed information function of Dobson cyclone data

F.3. Finding the MLE using the Newton-Raphson algorithm

F.3.1. Iterative maximization

(c.f., Dobson and Barnett (2018), Chapter 4)

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:

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

The reasoning for this algorithm is that we can approximate the score function near $\hat{\theta}^*$ using the first-order Taylor polynomial[7]:

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

---

[7] 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: this substitution 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)):

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

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

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

$$\left\{ \mathfrak{I}_{jk} \stackrel{\text{def}}{=} Cov\left(\ell'_j, \ell'_k\right) = E[\ell_j' \ell_k'] - E[\ell'_j] E[\ell'_k] \right\}$$

$I_e(\theta, y)$ is sometimes computationally easier to compute for Newton-Raphson-type maximization algorithms.

c.f. https://en.wikipedia.org/wiki/Newton%27s_method_in_optimization

---

Example F.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 F.16, we found that the score function was:

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

In Exercise F.18, we found that the Hessian was:

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

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

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

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

[8] https://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("l'(lambda)") +
  xlab("lambda") +
  geom_hline(yintercept = 0)

print(plot1)
```

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

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

```r
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("l'(lambda)") +
  xlab("lambda")

print(plot_loglik)
```

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:

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

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

```
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 F.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),
      col = "new estimate"
    )
  )
```

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

---

We repeat this process until the likelihood converges:

Compare with Exercise F.23

Table F.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( # nolint: object_name_linter
  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( # nolint: object_name_linter
    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) # nolint: object_name_linter

  cur_lambda_est <- new_lambda_est

  if (abs(diff_loglik) < tolerance) {
    break
  }
}

NR_info
#> # A tibble: 6 x 7
#>   iteration  lambda likelihood `log(likelihood)`    score hessian `diff(loglik)`
#>       <dbl> <num:.>      <dbl>         <num:.4!>    <dbl>   <dbl>          <dbl>
#> 1         0  3.0000   4.00e-18          -40.0610 1.1 e+ 1   -8         NA
#> 2         1  4.3750   4.33e-14          -30.7708 3.46e+ 0   -3.76       9.29e+ 0
#> 3         2  5.2941   2.57e-13          -28.9897 6.00e- 1   -2.57       1.78e+ 0
#> 4         3  5.5277   2.76e-13          -28.9176 2.54e- 2   -2.36       7.21e- 2
#> 5         4  5.5384   2.76e-13          -28.9175 4.93e- 5   -2.35       1.37e- 4
#> 6         5  5.5385   2.76e-13          -28.9175 1.87e-10   -2.35       5.18e-10
```

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

Figure F.13.: Newton-Raphson algorithm for finding MLE of model F.13 for `cyclone` data

F.4. Maximum likelihood inference for univariate Gaussian models

Suppose $X_1, ..., X_n \sim_{\text{iid}} N(\mu, \sigma^2)$. Let $X = (X_1, \dots, X_n)^\top$ 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.

$$\mathcal{L} = \prod_{i=1}^{n} (2\sigma^2\pi)^{-1/2} \exp\left\{ -\frac{1}{2} \frac{(x_i - \mu)^2}{\sigma^2} \right\}$$

Then the log-likelihood is:

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

F.4.1. The score function

$$\ell'(x,\theta) \stackrel{\text{def}}{=} \frac{\partial}{\partial\theta}\ell(x,\theta) = \begin{pmatrix} \frac{\partial}{\partial\mu}\ell(\theta;x) \\ \frac{\partial}{\partial\sigma^2}\ell(\theta;x)\end{pmatrix} = \begin{pmatrix} \ell'_\mu(\theta;x) \\ \ell'_{\sigma^2}(\theta;x)\end{pmatrix}$$

.

$\ell'(x,\theta)$ is the function we set equal to 0 and solve to find the MLE:

$$\hat{\theta}_{ML} = \{\theta : \ell'(x,\theta) = 0\}$$

F.4.2. MLE of μ

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

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 $\hat{\mu}_{ML} = \overline{x}$.

F.4.3. 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.

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

$$= -\frac{n}{2}\left(\sigma^2\right)^{-1} + \frac{1}{2}\left(\sigma^2\right)^{-2}\sum_{i=1}^{n}(x_i-\mu)^2$$

If $\frac{d\ell}{d\sigma^2} = 0$, then:

$$\frac{n}{2}\left(\sigma^2\right)^{-1} = \frac{1}{2}\left(\sigma^2\right)^{-2}\sum_{i=1}^{n}\left(x_i-\mu\right)^2$$

$$\sigma^2 = \frac{1}{n}\sum_{i=1}^{n}\left(x_i-\mu\right)^2$$

We plug in $\hat{\mu}_{ML} = \overline{x}$ to maximize globally (a technique called profiling):

$$\hat{\sigma}^2_{ML} = \frac{1}{n}\sum_{i=1}^{n}\left(x_i-\overline{x}\right)^2$$

Now:

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

Evaluated at $\mu = \overline{x}, \sigma^2 = \frac{1}{n}\sum_{i=1}^{n}\left(x_i-\overline{x}\right)^2$, we have:

$$\begin{aligned}
\frac{d^2\ell}{\left(d\sigma^2\right)^2} &= \left(\hat{\sigma}^2\right)^{-2}\left\{\frac{n}{2} - \left(\hat{\sigma}^2\right)^{-1}\sum_{i=1}^{n}\left(x_i-\overline{x}\right)^2\right\} \\
&= \left(\hat{\sigma}^2\right)^{-2}\left\{\frac{n}{2} - \left(\hat{\sigma}^2\right)^{-1} n\hat{\sigma}^2\right\} \\
&= \left(\hat{\sigma}^2\right)^{-2}\left\{\frac{n}{2} - n\right\} \\
&= \left(\hat{\sigma}^2\right)^{-2} n\left\{\frac{1}{2} - 1\right\} \\
&= \left(\hat{\sigma}^2\right)^{-2} n\left(-\frac{1}{2}\right) < 0
\end{aligned}$$

Finally, we have:

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

Evaluated at $\mu = \hat{\mu} = \overline{x}, \sigma^2 = \hat{\sigma}^2 = \frac{1}{n}\sum_{i=1}^{n}(x_i - \overline{x})^2$, we have:

$$\frac{d^2\ell}{d\mu\ d\sigma^2} = -\left(\hat{\sigma}^2\right)^{-2}(n\overline{x} - n\overline{x}) = 0$$

F.4.4. Covariance matrix

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

So:

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

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

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

To prove it's a maximum, we need:

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

F.5. 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.

The "heart and estrogen/progestin study" (HERS) was 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 non-diabetics 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 F.4.: HERS dataset

```
hers |> head()
#> # A tibble: 6 x 37
#>   HT              age raceth  nonwhite smoking drinkany exercise physact globrat
#>   <dbl+lbl>     <dbl> <dbl+l> <dbl+lb> <dbl+l> <dbl+lb> <dbl+lb> <dbl+l> <dbl+l>
#> 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]  0 [no]   0 [no]   1 [muc~ 3 [goo~
#> 3 1 [hormone t~    69 1 [Whi~ 0 [no]   0 [no]  0 [no]   0 [no]   3 [abo~ 3 [goo~
#> 4 0 [placebo]      64 1 [Whi~ 0 [no]   1 [yes] 1 [yes]  0 [no]   1 [muc~ 3 [goo~
#> 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 # 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)
plot1 <-
  data1 |>
  ggplot(aes(x = glucose)) +
  geom_histogram(aes(x = glucose, after_stat(density))) +
  theme_classic()

print(plot1)
```

Looks somewhat plausibly Gaussian. Good enough for this example!

F.5.1. 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.

F.5.2. 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 default inputs
    # 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(...))
```

F.5.3. Graph the Likelihood as a function of μ

(fixing σ^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")
```

F.5.4. Graph the Log-likelihood as a function of μ

(fixing σ^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")
```

F.5.5. 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)")
```

F.5.6. Standard errors by sample size:

Recall from Section F.4.4 that the asymptotic standard error of $\hat{\mu}_{ML}$ is

$$\begin{aligned}\widehat{\mathrm{SE}}(\hat{\mu}) &= \sqrt{\left[\left(\hat{\mathcal{I}}(\hat{\mu}_{ML})\right)^{-1}\right]} \\ &= \frac{\hat{\sigma}}{\sqrt{n}}\end{aligned}$$

```
se_mu_hat <- function(n, sigma = sd(glucose_data)) sigma / sqrt(n)
ggplot() +
  geom_function(fun = se_mu_hat) +
  scale_x_log10(
    limits = c(10, 10^5), name = "Sample size",
    labels = scales::label_comma()
  ) +
  ylab("Standard error of mu (mg/dl)") +
  theme_classic()
```

F.5.7. Power

F.5.7.1. Rejection region

For example, suppose we wish to detect a difference from the hypothesized value $\mu_0 = 95$. We reject the null hypothesis for any mean value outside the "non-rejection interval"

$$\mu_0 \pm F^{-1}_{t(n-1)}(1-\alpha/2)\sqrt{\frac{\sigma^2}{n}}$$

```
mu_0 <- 95
n <- length(glucose_data)
se <- se_mu_hat(n = n)
margin <- qt(0.975, df = n - 1) * se
upperbound <- mu_0 + margin
lowerbound <- mu_0 - margin
```

In this case, the non-rejection interval is $[92.959028, 97.040972]$.

F.5.7.2. Calculate power under a simple alternative

Consider the simple alternative that the true value is actually the estimated mean calculated from the data (i.e. 98.66). Let's also assume that the known standard deviation is what we estimated from the data.

```
prob_low <- pt(
  q = (lowerbound - mu_hat) / se,
  df = n - 1,
  lower.tail = TRUE
)
```

```
prob_high <- pt(
  q = (upperbound - mu_hat) / se,
  df = n - 1,
  lower.tail = FALSE
)

power <- prob_low + prob_high
print(power)
#> [1] 0.940662
```

F.5.7.3. Power as a function of sample size

```
power <- function(n = 100, null = 95, alt = 98.66) {
  # there's no such thing as fractional sample size:
  n <- floor(n)
  # using the function we wrote earlier:
  se <- se_mu_hat(n = n)
  reject_upper <- ((null + qt(0.975, df = n - 1) * se) - alt) / se
  reject_lower <- ((null - qt(0.975, df = n - 1) * se) - alt) / se
  p_reject_high <-
    pt(
      q = reject_lower,
      df = n - 1
    )
  p_reject_low <-
    pt(
      q = reject_upper,
      df = n - 1,
      lower = FALSE
    )
  p_reject <- p_reject_high + p_reject_low
  return(p_reject)
}
power_plot <-
  ggplot() +
  geom_function(fun = power, n = 100) +
  xlim(c(2, 200)) + # n = 1 is not allowed for t-distribution
  ylim(0, 1) +
  ylab("Power") +
  xlab("n") +
  theme_bw()
print(power_plot)
```

F.5.8. Simulations

F.5.8.1. 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),
  mu_0 = mean(glucose_data) * 0.9,
  sigma2 = var(glucose_data),
  return_data = FALSE # if this is set to true, we will create a list()
  # containing both 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 - mu_0) / 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

  # 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     97.4        9.48  0.948         95.5          99.3  9.09 1.04e-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)
mu_0 <- 80
sim_output <- do_one_sim(mu_0 = mu_0, return_data = TRUE)
our_results <-
  sim_output$results |>
  mutate(source = "`do_one_sim()`")

results_t_test <- t.test(sim_output$data, mu = mu_0)

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~     99.8        9.24  0.924         97.9          102.  21.4 6.23e-39
#> 2 `stats:~     99.8        9.24  0.924         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!

F.5.8.2. 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_sim_once` function
) {
  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) # sets a different seed for each simulation iteration,
    # to get a different dataset each time

    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 = 1000,
  mu = mean(glucose_data),
  sigma2 = var(glucose_data),
  n = 100 # this is the number of samples per simulated data set
)

sim_results
#> # A tibble: 1,000 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     99.7        9.40  0.940         97.8         102.  11.6
#>  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          7    100.         9.86  0.986         98.1         102.  11.5
#>  8          8     97.7       11.1   1.11          95.5          99.9  8.03
#>  9          9     98.1        9.86  0.986         96.2         100.   9.45
#> 10         10     97.3        9.68  0.968         95.3          99.2  8.74
#> # i 990 more rows
#> # 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.

F.5.8.3. 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(.data$`mu-hat`) - mu,
      `SE(mu-hat)` = sd(.data$`mu-hat`),
      `bias[SE-hat]` = mean(.data$se_hat) - se_mu_hat,
      `SE(SE-hat)` = sd(.data$se_hat),
      coverage = mean(.data$`confint covers true mu`),
      power = mean(.data$`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       -0.00501         1.00       -0.00113       0.0736    0.959     1
```

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…

F.6. likelihood graphs

```
library(pander)
library(ggplot2)
library(plotly)
library(dplyr)
library(haven)
```

```
# load the data from package
hers = haven::read_dta(fs::path_package("rme", "extdata/hersdata.dta"))
# "https://regression.ucsf.edu/sites/g/files/tkssra16191/files/wysiwyg/home/data/hersdata.d
```

```
data1 =
  hers |>
  filter(
    diabetes == 0,
    exercise == 0)

n.obs <- nrow(data1)


glucose_data =
  data1 |>
  pull(glucose)

plot1 =
  data1 |>
  ggplot() +
  geom_histogram(aes(x = glucose), bins = 30) +
  theme_classic()

plot1 |> ggplotly()
```

Looks somewhat plausibly Gaussian. Good enough for this example!

F.7. Construct the likelihood and log-likelihood functions

```
# it's computationally better to construct the log-likelihood first and then
# exponentiate it to get the likelihood
```

```
loglik = function(
    mu = mean(x), # 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(...))
```

F.7.1. Graph the Likelihood

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

Figure F.14.: Likelihood of `hers` data w.r.t. μ

F.7.2. Graph the Log-likelihood

```
ggplot() +
  geom_function(fun = function(x) loglik(mu = x)) +
  xlim(mean(glucose_data) + c(-1,1) * sd(glucose_data)) +
  ylab('log(likelihood)') +
  xlab("mu") +
  geom_vline(xintercept = mean(glucose_data), col = "red")
```

Figure F.15.: Log-likelihood of `hers` data w.r.t. μ

F.8. Likelihood and log-likelihood for σ^2, conditional on $\mu = \hat{\mu}$:

```
lik_plot = 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") +
  ylab('Likelihood')
```

```
loglik_plot = 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") +
ylab("log(likelihood)")
```

```r
## Graph the log-likelihood ranging over both parameters at once:

library(plotly)

n_points = 25
mu = seq(90, 105, length.out = n_points)
sigma = seq(6, 20,
            length.out = n_points)
names(mu) = round(mu, 5)
names(sigma) = round(sigma, 5)
lliks = outer(mu, sigma, loglik)
liks = outer(mu, sigma, lik)

plotly::plot_ly(
  type = "surface",
  x = ~mu,
  y = ~sigma,
  z = ~t(lliks))
```

G. Introduction to Bayesian inference

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(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' = 6)

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 default
legend_text_size = 9
run_graphs = TRUE
```

Suppose $X_1, ..., X_n \sim_{\text{iid}} N(M, 1)$

Suppose $M \sim N(0, 1)$.

Then:

$$\begin{aligned} p(M = \mu | X = x) &\propto p(M = \mu, X = x) \\ &= p(X = x | M = \mu) p(M = \mu) \\ &\propto \exp\left\{-\frac{1}{2} n\mu^2 - 2\mu n \bar{x}\right\} \exp\left\{-\frac{1}{2}\mu^2\right\} \\ &= \exp\left\{-\frac{1}{2}(n+1)\mu^2 - 2\mu n \bar{x}\right\} \\ &\propto \exp\left\{-\frac{1}{2}(n+1)(\mu - \frac{n}{n+1}\bar{x})^2\right\} \end{aligned}$$

So:

$$p(M = \mu | X = x) \sim N(\frac{n}{n+1}\bar{x}, (n+1)^{-1})$$

Let's put this in perspective.

Here's a frequentist CI:

```
set.seed(1)
mu <- 2
sigma <- 1
n <- 20
x <- rnorm(n = n, mean = mu, sd = sigma)
xbar <- mean(x)
se <- sigma / sqrt(n)
CI_freq <- xbar + se * qnorm(c(.025, .975))
print(CI_freq)
#> [1] 1.75226 2.62879
```

```
lik0 <- function(mu) dnorm(x = x, mean = mu, sd = 1) |> prod()
lik <- function(mu) {
  (2 * pi * sigma^2)^(-n / 2) *
    exp(
      -1 / (2 * sigma^2) *
        (sum(x^2) - 2 * mu * sum(x) + n * (mu^2))
    )
}
library(ggplot2)
ngraph <- 1001
plot1 <- ggplot() +
  geom_function(fun = lik, aes(col = "likelihood"), n = ngraph) +
  xlim(c(-5, 10)) +
  theme_bw() +
  labs(col = "") +
  theme(legend.position = "bottom")
print(plot1)
```

Here's a Bayesian CI:

```
mu_prior_mean <- 0
mu_prior_sd <- 1
mu_post_mean <- n / (n + 1) * xbar
mu_post_var <- 1 / (n + 1)
mu_post_sd <- sqrt(mu_post_var)
CI_bayes <- qnorm(
  p = c(.025, .975),
  mean = mu_post_mean,
  sd = mu_post_sd
)
print(CI_bayes)
```

```
#> [1] 1.65851 2.51391
prior <- function(mu) dnorm(mu, mean = mu_prior_mean, sd = mu_prior_sd)
posterior <- function(mu) dnorm(mu, mean = mu_post_mean, sd = mu_post_sd)
plot2 <- plot1 +
  geom_function(fun = prior, aes(col = "prior"), n = ngraph) +
  geom_function(fun = posterior, aes(col = "posterior"), n = ngraph)
print(plot2 + scale_y_log10())
```

Here's $p(M \in (l(x), r(x)) | X = x)$:

```
pr_in_CI <- pnorm(
  CI_freq,
  mean = mu_post_mean,
  sd = mu_post_sd
) |> diff()
print(pr_in_CI)
#> [1] 0.930583
```

G.1. Other resources

UC Davis courses

- STA 015C[1]: "Introduction to Statistical Data Science III"
- STA 035C[2]: "Statistical Data Science III"
- STA 145[3]: "Bayesian Statistical Inference"
- ECL 234[4]: "Bayesian Models - A Statistical Primer"

[1] https://catalog.ucdavis.edu/search/?q=STA+015C
[2] https://catalog.ucdavis.edu/search/?q=STA+035C
[3] https://catalog.ucdavis.edu/search/?q=STA+145
[4] https://catalog.ucdavis.edu/search/?q=ECL+234

- PLS 207[5]: "Applied Statistical Modeling for the Environmental Sciences"
- PSC 205H[6]: "Applied Bayesian Statistics for Social Scientists"
- POL 280[7]: "Bayesian Methods: for Social & Behavioral Sciences"
- BAX 442[8]: "Advanced Statistics"

Books

- Ross (2022) is a free online textbook
- "Population health thinking with Bayesian networks" (Tomas J. Aragon 2018) is on my to-read list
- McElreath (2020)
  - very popular recently
  - author used to be a UCD professor
  - ECL 234[9] uses this book
  - videos: https://www.youtube.com/playlist?list=PLDcUM9US4XdPz-KxHM4XHt7uUVGWWVSus
  - course materials: https://github.com/rmcelreath/stat_rethinking_2024
- Korner-Nievergelt and Korner-Nievergelt (2015)
- Cowles (2013)
- Kéry, Schaub, and Beissinger (2012)
- Hobbs and Hooten (2015) has been used in PLS 207[10]

[5] https://catalog.ucdavis.edu/search/?q=PLS+207
[6] https://catalog.ucdavis.edu/search/?q=PSC+205H
[7] https://catalog.ucdavis.edu/search/?q=POL+280
[8] https://catalog.ucdavis.edu/search/?q=BAX+442
[9] https://catalog.ucdavis.edu/search/?q=ECL+234
[10] https://catalog.ucdavis.edu/search/?q=PLS+207

H. 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(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' = 6)

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 default
legend_text_size = 9
run_graphs = TRUE
```

H.1. Parameters versus random variables

The parameters of a probability distribution shouldn't involve the random variables being modeled:

This is wrong

$$X \sim Pois(\lambda)$$
$$\hat{\lambda}_{ML} \to_D N(\bar{X}, \lambda/n)$$

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.

H.2. R

H.2.1. Don't copy-paste code

Successful programmers don't use copy-paste! Write functions instead.[1]

H.3. Quarto

H.3.1. Separate divs and slide breaks

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

[1] https://r4ds.hadley.nz/functions#introduction

```
---
::: notes
:::
```

There needs to be an empty line between them:

```
---

::: notes
:::
```

H.3.2. `library(printr)` currently breaks `df-print: paged`

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

H.4. LaTeX

- don't use `align*` or `align*` in quarto; only `aligned`

Double superscript issues: https://www.overleaf.com/learn/latex/Errors/Double_superscript

I. Notation

Table I.1.: Notation used in this book

symbol	meaning	LaTeX
$\neg$	not	`\neg`
$\forall$	all	`\forall`
$\exists$	some	`\exists`
$\cup$	union, "or"	`\cup`
$\cap$	intersection, "and"	`\cap`
$\mid$	given, conditional on	`\mid`, `|`
$\sum$	sum	`\sum`
$\prod$	product	`\prod`
μ	mean	`\mu`
E	expectation	`\mathbb{E}`
$x^\top$	transpose of x	`x^{\top}`
$'$	transpose or derivative[1]	`'`
$\perp\!\!\!\perp$	independent	
$\therefore$	therefore, thus	`\therefore`
η	linear component of a GLM[2]	`\eta`
$\lfloor x \rfloor$	floor of x: largest integer smaller than x	`\lfloor x \rfloor`
$\lceil x \rceil$	ceiling of x: smallest integer larger than x	`\lceil x \rceil`

I.1. Information matrices

There is no consistency in the notation for observed and expected information matrices (see Table I.2).

Table I.2.: notation for information matrices

book	observed information	expected information
Dobson and Barnett (2018)	U'	$\mathfrak{I}$
Dunn and Smyth (2018)	$\mathfrak{I}$	$\mathcal{I}$
McLachlan and Krishnan (2007)	I	$\mathcal{I}$
Wood (2017)	$\hat{I}$	$\mathcal{I}$

[1] depending on whether it is applied to a matrix or a function

[2] https://en.wikipedia.org/wiki/Generalized_linear_model#:~:text=The%20linear%20predictor%20is%20the,data%20through%20the%20link%20function

These notes currently have a mixture of notations, depending on my whims and what reference I had last looked at. Eventually, I will try to standardize my notation to I for observed information and $\mathcal{I}$ for expected information.

I.2. Percent sign ("%")

The percent sign "%" is just a shorthand for "/100". The word "percent" comes from the Latin "per centum"; "centum" is Latin for 100, 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, just as $10\text{kg} = 10,000\text{g}$ is true and correct.

Proof.

$$\begin{aligned} 10\% &= 10/100 \\ &= \frac{10}{100} \\ &= 0.1 \end{aligned}$$

□

You are welcome to switch between decimal and percent notation freely; just make sure you execute it correctly.

I.3. Proofs

We can use any of:

- $\therefore$ (`\therefore` in LaTeX),
- $\Rightarrow$ (`\Rightarrow`),
- $\vDash$ (`\models`)

to denote logical entailments (deductive consequences).

Let's save $\rightarrow$ (`\rightarrow`) for convergence results.

I.4. Why is notation in probability and statistics so inconsistent and disorganized?

In grad school, we are asked to learn from increasingly disorganized materials and lectures. Not coincidentally, as the amount of organization decreases, the amount of complexity increases, the amount of difficulty increases, the number of reliable references decreases, and the amount of inconsistency in notation and content increases (both between multiple references and within single references!). In other words, as you approach the cutting-edge of most fields, you start to encounter into content that hasn't been fully thought through or standardized. This lack of clarity is unfortunate and undesirable, but it is understandable and inevitable.

It's worth noting that calculus was formalized in the 1600s[3], elementary algebra was formalized around 820[4], and arithmetic even earlier[5]. And calculus still has several competing notation systems[6]. In contrast, the field of statistics only emerged in the late 1800s and early 1900s[7], so it's not surprising that the notation and terminology is still developing. Generalized linear models were only formalized in 1972 (Nelder and Wedderburn (1972)), which is very recent in terms of the pace of scientific development[8].

[3] https://en.wikipedia.org/wiki/Leibniz%27s_notation
[4] https://en.wikipedia.org/wiki/Al-Jabr
[5] https://en.wikipedia.org/wiki/Arithmetic#History
[6] https://en.wikipedia.org/wiki/Notation_for_differentiation
[7] https://en.wikipedia.org/wiki/History_of_statistics#Development_of_modern_statistics
[8] https://en.wikipedia.org/wiki/The_Structure_of_Scientific_Revolutions

J. Statistical computing in R

J.1. Online R learning resources

There are an overwhelming number of great resources for learning R; here are some recommendations:

- *The RStudio Education website*[1], especially:
  - *Finding your way to R*[2]
- *R for Epidemiology* (Cannell and Livingston (2024))
- *The Epidemiologist R Handbook* (Batra (2024))
- *Practical R for Epidemiologists* (Myatt (2022))
- *R for Data Science* (Wickham, Çetinkaya-Rundel, and Grolemund (2023))
- *Advanced R* (Wickham (2019))
- *R Graphics Cookbook* (Chang (2024))
- *R Packages* (Wickham and Bryan (2023))
- Nahhas (2023) (same author as Nahhas (2024))
- Myatt (2022)
- Tomas J. Aragon (2017) (previously Tomas J. Aragon (2013)): Author is State Public Health Officer and Director, California Department of Public Health, https://drtomasaragon.github.io/)
- *SAS and R* (Kleinman and Horton (2009))
- The "sassy system"[3] is "an integrated set of packages designed to make programmers more productive in R, particularly those with a background in SAS® software. The system leverages useful concepts and thought patterns to create a more efficient and satisfactory R programming experience."
  - In particular, the procs[4] package in R provides versions of common SAS procedures, such as 'proc freq', 'proc means', 'proc ttest', 'proc reg', 'proc transpose', 'proc sort', and 'proc print'
- *R for SAS and SPSS users* (Muenchen (2011))
- *Building reproducible analytical pipelines with R* (Rodrigues (2023))
- *Posit Recipes: Some tasty R code snippets*: https://posit.cloud/learn/recipes

J.2. UC Davis R programming courses

There are several dedicated UC Davis courses on R programming:

[1] https://education.rstudio.com
[2] https://education.rstudio.com/learn/
[3] https://r-sassy.org/
[4] https://cran.r-project.org/web/packages/procs/

- BIS 015L[5]: Introduction to Data Science for Biologists
  - see course materials at https://jmledford3115.github.io/datascibiol/
- ENV 224[6]/ ECL 224[7]: Data Management & Visualization in R
  - see lecture videos and course materials at https://ucd-r-davis.github.io/R-DAVIS/
- ESP 106[8]: Environmental Data Science
- STA 015B[9]: Introduction to Statistical Data Science II
- STA 032[10]: Gateway to Statistical Data Science
- STA 035A[11]: Statistical Data Science
- STA 035B[12]: Statistical Data Science II
- STA 141A[13]: Fundamentals of Statistical Data Science
- STA 242[14]: Introduction to Statistical Programming
- ABG 250[15]: Mathematical Modeling in Biological Systems
- **PSC 203A[16]** "Data Cleaning & Management in the Social Sciences"
- PSC 203B[17] "Data Visualization in the Social Sciences"

DataLab[18] maintains another list of courses: https://datalab.ucdavis.edu/courses/

DataLab also provides short-form workshops on R programming and data science: https://datalab.ucdavis.edu/workshops/

J.3. Demographics tables

Demographics tables are important first steps in many data analyses and papers.

The `gtsummary` package is flexible and can probably provide whatever table options you're looking for, and if not, the developers are usually very welcoming of feature requests.

If `gtsummary` is really not doing what you want, other packages I've used for demographics tables include:

- https://cran.r-project.org/web/packages/procs/ (replicates common SAS commands)
- https://cran.r-project.org/web/packages/arsenal/index.html (from the Mayo Clinics)
- https://cran.r-project.org/web/packages/table1/index.html

[5] https://catalog.ucdavis.edu/search/?q=BIS+015L
[6] https://catalog.ucdavis.edu/search/?q=ENV+224
[7] https://catalog.ucdavis.edu/search/?q=ECL+224
[8] https://catalog.ucdavis.edu/search/?q=ESP+106
[9] https://statistics.ucdavis.edu/expanded-descriptions/15b
[10] https://statistics.ucdavis.edu/expanded-descriptions/32
[11] https://statistics.ucdavis.edu/expanded-descriptions/35A
[12] https://statistics.ucdavis.edu/expanded-descriptions/35B
[13] https://statistics.ucdavis.edu/expanded-descriptions/141A
[14] https://statistics.ucdavis.edu/expanded-descriptions/242
[15] https://catalog.ucdavis.edu/search/?q=ABG+250
[17] https://catalog.ucdavis.edu/search/?q=PSC+203B
[18] https://datalab.ucdavis.edu/

J.4. Writing functions

- Read this ASAP: https://r4ds.hadley.nz/functions.html
- Use this as a reference: https://adv-r.hadley.nz/functions.html

J.4.1. Methods versus functions

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

J.4.2. Debugging code

- https://adv-r.hadley.nz/debugging.html
- https://www.maths.ed.ac.uk/~swood34/RCdebug/RCdebug.html

J.5. `data.frames` and `tibbles`

J.5.1. Displaying `tibbles`

See `vignette("digits", package = "tibble")`

J.6. 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 Wickham[19] and his colleagues at posit[20][21].

Details:

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

[19] https://hadley.nz/
[20] https://posit.co/
[21] the company formerly known as RStudio[22]

J.7. Piping

See Wickham, Çetinkaya-Rundel, and Grolemund (2023)[23] for details.

There are currently (2025) two commonly-used pipe operators in R:

- `%>%`: the "`magrittr` pipe", from the `magrittr`[24] package (Bache and Wickham (2022); re-exported[25] by `dplyr`[26] and others) .
- `|>`: the "native pipe", from base R ($\geq$ 4.1.0)

See https://www.tidyverse.org/blog/2023/04/base-vs-magrittr-pipe for a comparison of their behavior.

J.7.1. Which pipe should I use?

Wickham, Çetinkaya-Rundel, and Grolemund (2023) recommends the native pipe[27]:

> 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.

J.7.2. 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

[23] https://r4ds.hadley.nz/data-transform.html#sec-the-pipe
[24] https://cran.r-project.org/web/packages/magrittr/index.html
[25] https://r-pkgs.org/dependencies-in-practice.html#re-exporting
[26] https://cran.r-project.org/web/packages/dplyr/index.html
[27] https://r4ds.hadley.nz/data-transform.html#sec-the-pipe:~:text=So%20why%20do%20we%20recommend%20the%20base%20pipe%3F

J.8. 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/
- Learn LaTeX in 30 minutes (not everything in here is relevant to Quarto): https://www.overleaf.com/learn/latex/Learn_LaTeX_in_30_minutes
- LaTeX symbol reference guide: https://oeis.org/wiki/List_of_LaTeX_mathematical_symbols
- LaTeX commands: https://www.overleaf.com/learn/latex/Commands

To compile Quarto documents to pdf, run these commands first:

```
install.packages("tinytex")
tinytex::install_tinytex()
```

See Knuth (1984) for additional discussion of literate programming.

J.9. One source file, multiple outputs

One of quarto's excellent features is the ability to convert the same source file into multiple output formats; in particular, I am using the same set of source files to generate an html website, a pdf document, and a set of revealjs slide decks.

I use `::: notes` divs to mark text chunks to omit from the revealjs format but include in the website and pdf format.

J.10. 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%20structure.
- Read this ASAP: https://r-pkgs.org/whole-game.html
- Use the rest of Wickham and Bryan (2023) as a reference

J.11. Submitting packages to CRAN

- Read this first: https://r-pkgs.org/release.html
- A problems-and-solutions book is under construction: https://contributor.r-project.org/cran-cookbook/

J.12. Git

94% of respondents to a 2022 Stack Overflow survey[28] reported using git for version control.

More details[29]

- *Happy Git with R* https://happygitwithr.com/
- https://usethis.r-lib.org/articles/pr-functions.html
- *Git Magic* http://www-cs-students.stanford.edu/~blynn/gitmagic/
- https://ohshitgit.com/
- https://maelle.github.io/saperlipopette/

J.13. Spatial data science

- Pebesma and Bivand (2023)

J.14. Shiny apps

- Read Wickham (2021) first
- Use Fay et al. (2021) as a reference

J.15. Making the most of RStudio

Over time, explore all the tabs and menus; there are a lot of great quality-of-life features.

- use the `History` tab to view past commands; you can rerun them or copy them into a source code file in one click! (up-arrow in the Console also enables this process, but less easily).

J.16. Contributing to R

Many modern R packages are developed on Github, and welcome bug reports and pull requests (suggested edits to source code) through the Github interface.

To contribute to "base R" (the core systems), see https://contributor.r-project.org/

[28] https://survey.stackoverflow.co/2022/#section-version-control-version-control-systems
[29] https://r-pkgs.org/software-development-practices.html#sec-sw-dev-practices-git-github

K. Contributing to `rme`

Contributions to these notes are very much appreciated; anything from one-character typo corrections to new chapters or rewrites. The GitHub repository for this project[1] provides a Pull Request system for submitting contributions. See https://happygitwithr.com/pr-extend for an explanation of the pull request system and the available R utility functions for working with pull requests.

K.1. Style guide

- Every abstract concept (definition or theorem) should have at least one concrete example immediately following it.
- More structure (headers, labels) is better.
- Make each conceptual chunk as compact as possible:
  - Decompose large, complicated, difficult concepts into smaller, simpler, and easier pieces.
  - Decompose long derivations into smaller lemmas.
  - When manipulating part of a larger expression, isolate that part in a lemma.
- Add slide breaks[2] between exercises/theorems and solutions/proofs

K.2. Fixing typos

This book is written using Quarto[3]. 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.

K.3. 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.

[1] https://github.com/d-morrison/rme
[2] https://quarto.org/docs/presentations/revealjs/#creating-slides
[3] https://quarto.org/docs/books/

K.3.1. Pull request[4] 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.

K.3.2. Code style

- New code should follow the tidyverse style guide[5]. You can use the styler[6] package to apply these styles, but please don't restyle code that has nothing to do with your PR.

K.4. Code of Conduct

Please note that the `rme` project is released with a Contributor Code of Conduct[7]. By contributing to this project you agree to abide by its terms.

K.5. Additional references

For a detailed discussion on contributing to this and other projects, please see the Tidyverse development contributing guide[8] and the Tidyverse code review principles[9]. This project is not part of the tidyverse, but we have borrowed their development processes.

[4] https://usethis.r-lib.org/articles/pr-functions.html#whats-a-pull-request
[5] https://style.tidyverse.org
[6] https://CRAN.R-project.org/package=styler
[7] CODE_OF_CONDUCT.md
[8] https://rstd.io/tidy-contrib
[9] https://code-review.tidyverse.org/

L. Exam formula sheet

L.1. Epi 202: Probability

$$\begin{aligned}\mathrm{Var}\big(\tilde{a}\cdot\tilde{X}\big) &= \mathrm{Var}\left(\sum_{i=1}^{n} a_i X_i\right)\\ &= \tilde{a}^\top \mathrm{Var}\big(\tilde{X}\big)\tilde{a}\\ &= \sum_{i=1}^{n}\sum_{j=1}^{n} a_i a_j \mathrm{Cov}\big(X_i, X_j\big)\end{aligned}$$

L.2. Epi 203: Statistical inference

$$\mathcal{L}(\theta) \stackrel{\text{def}}{=} \mathrm{p}(\tilde{X}=\tilde{x}|\Theta=\theta)$$

$$\ell \stackrel{\text{def}}{=} \log\{\mathcal{L}(\tilde{x}|\theta)\}$$

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

$$\ell'' \stackrel{\text{def}}{=} \frac{\partial}{\partial\tilde{\theta}}\frac{\partial}{\partial\tilde{\theta}^\top}\ell(\tilde{x}|\tilde{\theta})$$

$$\ell''_{ij} = \frac{\partial}{\partial\theta_i}\frac{\partial}{\partial\theta_j}\ell(\tilde{X}=\tilde{x}|\tilde{\theta})$$

$$I \stackrel{\text{def}}{=} -\ell''(\tilde{x}|\tilde{\theta})$$
$$\mathcal{J} \stackrel{\text{def}}{=} \mathrm{E}[I(\tilde{x}|\theta)]$$

$$\hat{\theta}_{ML} \dot{\sim} \mathrm{N}\Big(\theta, \big[\mathcal{J}(\tilde{\theta})\big]^{-1}\Big)$$

L.3. Epi 204: Generalized linear models

Generalized linear models have three components:

1. The **outcome distribution** family: $\mathrm{p}(Y|\mu(\tilde{x}))$
2. The **link function**: $g(\mu(\tilde{x})) = \eta(\tilde{x})$
3. The **linear component**: $\eta(\tilde{x}) = \tilde{x} \cdot \beta$

$$\left[\pi \stackrel{\text{def}}{=} \Pr(Y=1|\tilde{X}=\tilde{x})\right] \underbrace{\overbrace{\underset{\frac{\omega}{1+\omega}}{\overset{\frac{\pi}{1-\pi}}{\rightleftarrows}} \left[\omega \stackrel{\text{def}}{=} \text{odds}(Y=1|\tilde{X}=\tilde{x})\right] \underset{\exp\{\eta\}}{\overset{\log\{\omega\}}{\rightleftarrows}}}^{\text{logit}(\pi)}}_{\text{expit}(\eta)} \left[\eta(\tilde{x}) \stackrel{\text{def}}{=} \text{log-odds}(Y=1|\tilde{X}=\tilde{x})\right]$$

Figure L.1.: Diagram of logistic regression link and inverse link functions

$$\theta(\tilde{x}, \tilde{x}^*) = \exp\Big\{(\Delta\tilde{x}) \cdot \tilde{\beta}\Big\}$$

L.3.1. Estimates of odds ratios from 2x2 contingency tables

$$\hat{\theta} = \frac{ad}{bc}$$

L.3.2. Survival analysis

L.3.2.1. Probability distribution functions

Table L.1.: Probability distribution functions

Name	Symbols	Definition
Probability density function (PDF)	$\mathrm{f}(t), \mathrm{p}(t)$	$\mathrm{p}(T = t)$
Cumulative distribution function (CDF)	$\mathrm{F}(t), \mathrm{P}(t)$	$\mathrm{P}(T \leq t)$
Survival function	$\mathrm{S}(t), \bar{\mathrm{F}}(t)$	$\mathrm{P}(T > t)$
Hazard function	$\lambda(t), \mathrm{h}(t)$	$\mathrm{p}(T = t \mid T \geq t)$
Cumulative hazard function	$\Lambda(t), \mathrm{H}(t)$	$\int_{u=-\infty}^{t} \lambda(u)du$
Log-hazard function	$\eta(t)$	$\log\{\lambda(t)\}$

L.3.2.2. Diagram of survival distribution function relationships

$$\mathrm{f}(t) \xleftarrow[\mathrm{S}(t)\lambda(t)]{-S'(t)} \mathrm{S}(t) \xleftarrow{\exp\{-\Lambda(t)\}} \Lambda(t) \xleftarrow{\int_{u=0}^{t} \lambda(u)du} \lambda(t) \xleftarrow{\exp\{\eta(t)\}} \eta(t)$$

$$\mathrm{f}(t) \xrightarrow[\int_{u=t}^{\infty} \mathrm{f}(u)du]{\mathrm{f}(t)/\lambda(t)} \mathrm{S}(t) \xrightarrow[-\log \mathrm{S}(t)]{} \Lambda(t) \xrightarrow[\Lambda'(t)]{} \lambda(t) \xrightarrow[\log\{\lambda(t)\}]{} \eta(t)$$

L.3.2.3. Survival likelihood contributions, assuming non-informative censoring

$$\begin{aligned} \mathrm{p}(Y = y, D = d) &= [\mathrm{f}_T(y)]^d [\mathrm{S}_T(y)]^{1-d} \\ &= [\lambda_T(y)]^d [\mathrm{S}_T(y)] \end{aligned}$$

L.3.2.4. Nonparametric time-to-event distribution estimators

$$\hat{\lambda}_i = \frac{d_i}{n_i}$$

$$\hat{\mathrm{S}}_{KM}(t) \stackrel{\text{def}}{=} \prod_{\{i:\ t_i < t\}} \left[1 - \hat{\lambda}_i\right]$$

$$\hat{\Lambda}_{NA}(t) \stackrel{\text{def}}{=} \sum_{\{i:\ t_i < t\}} \hat{\lambda}_i$$

L.3.2.5. Proportional hazards model structure

Joint likelihood of data set: $\mathcal{L} \stackrel{\text{def}}{=} \mathrm{p}(\tilde{Y} = \tilde{y}, \tilde{D} = \tilde{d} | \mathbf{X} = \mathbf{x})$

Marginal likelihood contribution of obs. $\boldsymbol{i}$: $\mathcal{L}_i \stackrel{\text{def}}{=} \mathrm{p}(Y_i = y_i, D_i = d_i | \tilde{X}_i = \tilde{x}_i)$

Independent Observations Assumption: $\mathcal{L} = \prod_{i=1}^{n} \mathcal{L}_i$

Non-Informative Censoring Assumption: $T_i \perp\!\!\!\perp C_i | \tilde{X}_i$

$$\mathcal{L}_i \propto [\mathrm{f}_T(y_i|\tilde{x}_i)]^{d_i} [\mathrm{S}_T(y_i|\tilde{x}_i)]^{1-d_i} = \mathrm{S}_T(y_i|\tilde{x}_i) \cdot [\lambda_T(y_i|\tilde{x}_i)]^{d_i}$$

Survival function: $\mathrm{S}(t|\tilde{x}) \stackrel{\text{def}}{=} \mathrm{P}(T > t | \tilde{X} = \tilde{x}) = \int_{u=t}^{\infty} \mathrm{f}(u|\tilde{x}) du = \exp\{-\Lambda(t|\tilde{x})\}$

Probability density function: $\mathrm{f}(t|\tilde{x}) \stackrel{\text{def}}{=} \mathrm{p}(T = t | \tilde{X} = \tilde{x}) = -\mathrm{S}'(t|\tilde{x}) = \lambda(t|\tilde{x})\mathrm{S}(t|\tilde{x})$

Cumulative hazard function: $\Lambda(t|\tilde{x}) \stackrel{\text{def}}{=} \int_{u=0}^{t} \lambda(u|\tilde{x}) du = -\log\{\mathrm{S}(t|\tilde{x})\}$

Hazard function: $\lambda(t|\tilde{x}) \stackrel{\text{def}}{=} \mathrm{p}(T = t | T \geq t, \tilde{X} = \tilde{x}) = \Lambda'(t|\tilde{x}) = \frac{\mathrm{f}(t|\tilde{x})}{\mathrm{S}(t|\tilde{x})}$

Hazard ratio: $\theta(t|\tilde{x} : \tilde{x}^*) \stackrel{\text{def}}{=} \frac{\lambda(t|\tilde{x})}{\lambda(t|\tilde{x}^*)}$

Log-Hazard function: $\eta(t|\tilde{x}) \stackrel{\text{def}}{=} \log\{\lambda(t|\tilde{x})\} = \eta_0(t) + \Delta\eta(t|\tilde{x})$

Proportional Hazards Assumption:

$$\begin{aligned} \lambda(t|\tilde{x}) &= \lambda_0(t) \cdot \theta(\tilde{x}) \\ \Lambda(t|\tilde{x}) &= \Lambda_0(t) \cdot \theta(\tilde{x}) \\ \eta(t|\tilde{x}) &= \eta_0(t) + \Delta\eta(\tilde{x}) \end{aligned}$$

Logarithmic Link Function Assumption:

- **Link function**:

$$\log\{\lambda(t|\tilde{x})\} = \eta(t|\tilde{x})$$
$$\log\{\theta(\tilde{x})\} = \Delta\eta(\tilde{x})$$

- **Inverse link function**:

$$\lambda(t|\tilde{x}) = \exp\{\eta(t|\tilde{x})\}$$
$$\theta(\tilde{x}) = \exp\{\Delta\eta(\tilde{x})\}$$

Linear Predictor Component:

$$\eta(t|\tilde{x}) = \eta_0(t) + \Delta\eta(t|\tilde{x})$$
$$\Delta\eta(t|\tilde{x}) = \tilde{x} \cdot \tilde{\beta}$$

Linear Predictor Component Functional Form Assumption:

$$\Delta\eta(t|\tilde{x}) = \tilde{x} \cdot \tilde{\beta} \stackrel{\text{def}}{=} \beta_1 x_1 + \cdots + \beta_p x_p$$

L.3.2.6. Proportional hazards model partial likelihood formula:

$$\mathcal{L}_i^* = \frac{\theta(\tilde{x}_i)}{\sum_{k \in R(t_i)} \theta(\tilde{x}_k)}$$
$$\mathcal{L}^* = \prod_{\{i:\ d_i = 1\}} \mathcal{L}_i^*$$

L.3.2.7. Proportional hazards model baseline cumulative hazard estimator:

$$\hat{\Lambda}_0(t) = \sum_{t_i < t} \frac{d_i}{\sum_{k \in R(t_i)} \theta(x_k)}$$

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