

# Chapter 1

## A Taxonomy of Problems

The term “data science” has been overused in recent years, and it has become something of a buzzword as a result<sup>1</sup>. However, I think it can best be described as:

**data science:** Any endeavor in which statistics, machine learning, data analysis, computer science, and information science intersect with domain knowledge.

Data science is about using the machinery of statistics and computer science to solve real-world problems. In the clinical domain, that means incorporating methods from epidemiology, biostatistics, computer science, and machine learning with insights gained from the clinical research literature and the practical experiences of physicians, nurses, hospital administrators, operational teams, and biomedical researchers.

### 1.1 Project Examples

Whenever I teach, I ask students to provide some examples of projects for which they think data science could be useful. The following are real examples. They provide a broad representation of most of the types of problems clinicians and health system operations/population health teams are interested in.

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<sup>1</sup>See also: “artificial intelligence”, “machine learning”, “deep learning”.

1. *Unnecessary ER trips.* “Given a number of factors (types of admissions a person has had in the past, number of admissions/re-admissions, social determinants, etc.) can we predict who is going to show up at the emergency room unnecessarily”
2. *Good/poor candidates for program.* “determine if patients are good or poor candidates for one of our specialty care model bundle programs”
3. *Predicting unplanned admissions.* “predicting unplanned inpatient admissions based on many different variables (e.g. chronic conditions, engagement with primary care, etc.) and how these inputs interact with each other”
4. *Recommending an intervention.* “...stratification/prioritization of care management or other interventions or for clinical decision support...a tool would recommend an appropriate intervention based on the profile of the patient”
5. *Recommending a diagnosis.* “Based on unstructured chat conversations and also structured questions/forms/data...map out possible care pathways. For example, if someone says they have stomach pain, gives their zip code, insurance, pain tolerance and symptoms, and is logged in so we have past history, ask a few more questions and then we could determine they are 45% likely to have ulcer vs. constipation vs. food poisoning vs. appendicitis.”
6. *Predicting the amount paid by patients.* “Patient bill estimates - learning from claims data typical amount paid by patients for appointment reasons/types (e.g. estimate of additional services/care administered, and associated cost, based on patient details such as age, gender, etc.)”
7. *Identifying patient subtypes.* “identify cohorts within a population with chronic conditions based on their differences in longitudinal care across the continuum of settings (inpatient, ambulatory, primary care, specialty care, etc.)”
8. *Which conversations are similar?* “using previous chat histories to train (a chatbot) and become more effective/efficient for different, future patient chat experiences”

9. *Predictors of COVID-19 outcomes.* "Get baseline diabetes control marker (HbA1C) and acute glycemic control (inpatient glucose values) and see if either is a stronger predictor of COVID-19 outcomes (ICU, intubation, death)."
10. *Factors influencing mortality in myelofibrosis.* "We see lots of patients who are ineligible for clinical trials based on comorbidities and underlying organ dysfunction. However it is unclear how these factors affect OS. I would like to extract comorbidity data and baseline laboratory factors in patients with myelofibrosis to see how these factors affect mortality, if controlled for such important factors such as treatment, age, sex, insurance, number of comorbidities, and clinical risk score (DIPSS)."
11. *Non-adherence and difficult-to-treat asthma.* "We want to see whether non-adherence to prescribed inhaled corticosteroids plays a major role in poorly controlled asthma. Difficult-to-treat asthma can be evaluated by the number of ED visits, hospitalizations, prescriptions of prednisone and prescriptions of biological therapies. Using EPIC [we] can obtain medicine reconciliation information, of prescriptions sent, what proportion of those prescriptions were dispensed by Pharmacy. Question is can we find associations between the percentage of prescriptions filled and difficult-to-treat asthma."
12. *Impact of diabetes and hyperglycemia on progression-free survival.* "Aim: Assess the impact of diabetes and hyperglycemia on first-line systemic therapy response (progression-free survival) in patients with advanced non-small cell lung cancer. Diabetes- defined by presence of diagnosis codes coding for diabetes. Hyperglycemia- random glucose >200 ng/dL. Covariates of interest- age, sex, other treatments (RT, surgery), malignancy characteristics (stage, histology), smoking history, ecog (performance status), comorbidities, medications (steroids, anti-hyperglycemics)"
13. *Effect of statin use on MACE.* "Retrospective cohort study in elderly patients with CAD taking statins... exposed group are patients on a high-intensity statin; control group are patients on a moderate- or low-intensity statin. Participants matched based on age, gender, LDL category, and Elixhauser index category... The primary efficacy outcome

would be the time-to-first-event of 3-point MACE<sup>2</sup>.”

14. *Clustering patients with NAFLD.* “We wanted to understand non-alcoholic fatty liver disease (NAFLD) better, so we developed a cohort of NAFLD patients using EMR-based criteria and then clustered them based on comorbidities, medications, vital signs, and lab values to identify NAFLD subtypes. We then characterized the phenotypes and outcomes of the different subtypes.”

## 1.2 Abstracting the Problem

All of these examples describe situations where we want to use data to answer questions of clinical or operational importance. While the details differ in each scenario, the important thing to notice here is that many of the tasks themselves are structurally similar.

For example, all of the items except 7 – 8 and 14 describe situations where we want to associate information about a patient with a particular outcome or recommendation. Using information about a patient to estimate the size of a bill (#6) may appear to be a very different problem than uncovering factors influencing myelofibrosis mortality (#10), but the structure of the two problems is similar: the patient features are used as input, and the output is whatever quantity you care about (e.g. the cost to the patient in dollars or the probability of mortality by a certain timepoint).

Learning to see these types of similarities will give you a tremendous amount of power when attacking new problems in clinical data science. It will allow you to confidently deploy methods you used to solve one problem on a wide range of other problems. Each new method you learn then multiplies your capacity to solve problems, rather than adding to it.

### Question 1.1

How are items 7 – 8 and 14 different from the rest?

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<sup>2</sup>MACE stands for “Major Adverse Cardiac Event”. The 3-point MACE is a composite of nonfatal stroke, nonfatal myocardial infarction, and cardiovascular death.

**Question 1.2**

How are items 1 – 6 similar to items 9 – 13 and how are they different?

**Question 1.3**

How do items 1 – 3 differ from items 4 – 5 and how are they similar?

**Question 1.4**

How do items 1 – 3 differ from item 6? How is item 6 different from all of the other items?

**Question 1.5**

How do items 9 – 11 differ from items 12 – 13?

## 1.3 Terms and Contrasts

The basic ways in which clinical data science problems vary can be characterized using a few broad conceptual distinctions. These draw from both traditional clinical disciplines, like epidemiology, as well as machine learning/statistics.

### 1.3.1 Guidance vs. Understanding

Before beginning any study, it is important to carefully consider the study's goal and how the findings from the study will be used. This will help guide you in choosing appropriate methods. For example, in some studies we care mainly about using data to provide **guidance** that will enable us to perform our jobs better in the future. We may want to predict whether a patient is likely to experience an adverse outcome, or we may want to learn the type of patient who is most likely to benefit from a particular treatment. In these cases, we want the data to guide us in making better choices.

Now, contrast this with a study whose primary goal is scientific **understanding**. In this case, we care more about using data to improve our understanding of a phenomenon than in operationalizing those findings. For example, we may be interested in whether a particular genetic variant affects a phenotype, or we may want to establish a causal link between a particular treatment and an outcome.

The distinction is fuzzy and often imperfect, and the same kinds of methods can often be used in both cases. Depending on the goal, however, one may be willing to make certain compromises. For example, complex, “black box” predictive models (e.g. deep learning models) may be appropriate when the goal is guidance, but offer little in the way of understanding. Conversely, regression models have become the de facto standard for clinical trials and causal inference, but may not lead to optimal predictive ability. In situations where the primary goal is a rigorous understanding of causal relationships, that may not matter as much.

### 1.3.2 Observational Study vs. Experiment

In **experimental studies**, the investigator manipulates some aspect of the subjects’ experience and studies its effect on the outcome of interest. For example, here is the NIH’s definition of a **clinical trial**:

A research study in which one or more human subjects are prospectively assigned to one or more interventions (which may include placebo or other control) to evaluate the effects of those interventions on health-related biomedical or behavioral outcomes.

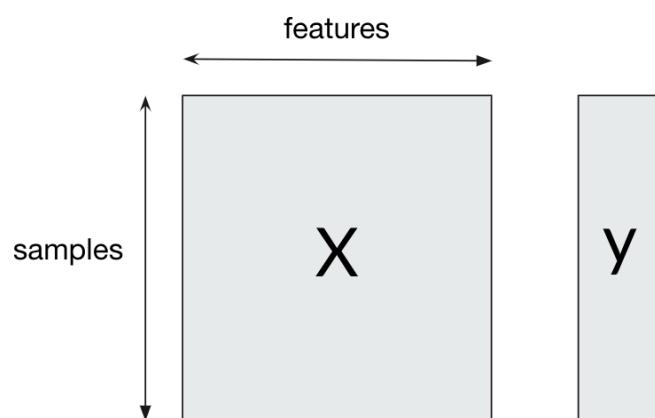
A clinical trial, therefore, is an experiment, because we control the intervention and monitor the effect of that intervention on one or more outcomes. Usually experimental studies employ some type of **randomization** to ensure that comparisons between different intervention groups are fair.

An **observational study**, in contrast, makes no attempt to interfere with its subjects. Instead, these individuals are simply observed, and inferences are made about the associations between different parameters and the outcome(s). Observational study designs and analytic plans are carefully designed to

minimize the effects of different sources of bias that can creep in due to lack of randomization. Although they're not usually referred to using this terminology, virtually all "big data" and machine learning oriented studies in healthcare are observational studies, because they use large datasets that were collected for other purposes.

### 1.3.3 Types of Machine Learning

This distinction, most often found in discussions of machine learning, refers to the way in which training data is applied to solve a problem. In **supervised learning**, the training data consist of pairs of input features and labels, and the algorithm learns to predict the value of the label from the input features. The general setup for supervised learning looks like this:



In **unsupervised learning**, only the input features are present (i.e. no  $y$ ) and the algorithm learns to recognize patterns, clusters, or other structure in the inputs. Although they're almost never referred to using this terminology, clinical studies that examine the effect between one or more exposures and an outcome are examples of supervised learning. Studies that attempt to uncover groups, or clusters, of similar patients or samples are examples of unsupervised learning.

There are also two other types of machine learning. In **semi-supervised learning**, a small amount of labeled data is used to create a much larger,

weakly-labeled set of training data that is then fed to a supervised learning algorithm. In **reinforcement learning**, an algorithm is trained with a reward system which provides feedback on the quality of the action the system performs in a given situation instead of (as in supervised learning) simply providing the “right answer”.

## Chapter 2

# The Basics of Classification

Classification is a form of supervised learning in which our goal is to learn a mapping between some features,  $x$ , and an output,  $y$ . In classification, the output,  $y$ , is a category. In **binary classification** (by far the most common), there are only two categories: yes or no, usually represented as “0” (no) or “1” (yes). In **multi-class classification**, there are more than two categories.

To learn an appropriate mapping, we feed **training data** to a **learning algorithm**. Different algorithms learn different types of mappings.

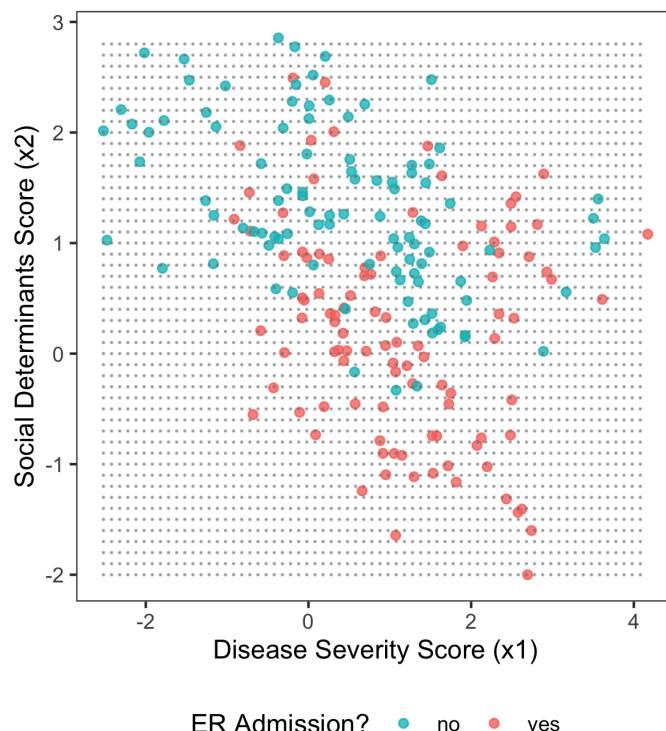
### 2.1 Definitions

- **Training data:** The data used, along with an appropriate learning algorithm, to create the mapping between input and output. It is composed of **training examples**, a.k.a. **samples**, each consisting of one or more input features and a single output.
- **Test data:** An independent dataset, not used in model training, on which the performance of a trained supervised learning model is evaluated.
- **Feature:** Also known as a **predictor**, or **covariate**, one of the inputs to a supervised learning algorithm.
- **Output:** Also known as the **outcome**, or **label**, the thing you are trying to predict.

- **Feature space:** Envisioning each feature as having its own axis that is orthogonal to all of the other features' axes, the multidimensional space spanned by those axes (or rather: unit vectors in the directions of those axes)
- **Extrapolation:** Making predictions outside the region of the feature space occupied by the training data. This will often lead to errors.

## 2.2 Visualizing the Classification Problem

Imagine we want to predict whether a patient will be readmitted to the emergency room (ER) within 30 days of hospital discharge. We gather data on two predictors: a disease severity score ( $x_1$ ), which characterizes the severity of illness, and a social determinants score ( $x_2$ ), which characterizes the patient's socioeconomic status. We have data on 200 patients.

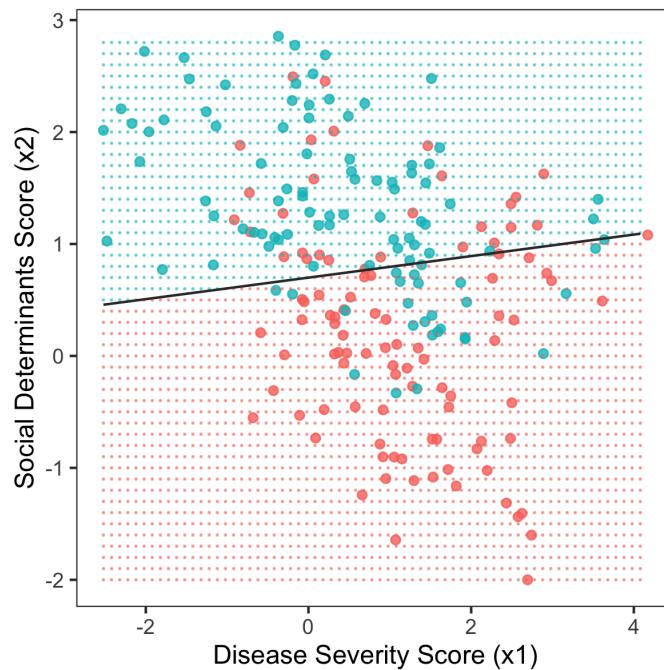


In this figure, the color refers to whether a patient was readmitted (blue = “no”, red = “yes”). The location of each point is governed by the patient’s disease severity score ( $x_1$ , horizontal axis) and social determinants score ( $x_2$ , vertical axis). Our goal in classification is to draw a **decision boundary** through this space, on one side of which we will predict that the patient is readmitted, and on the other side not.

## 2.3 Three Classification Algorithms

### 2.3.1 Logistic Regression

The simplest decision boundary is, arguably, a line. The logistic regression algorithm simply draws a line<sup>1</sup> through the feature space that divides the positive and negative training examples.




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<sup>1</sup>In a higher-dimensional feature space, the decision boundary for logistic regression is a **hyperplane**.

The output of a fitted logistic regression model from R looks like this:

```
```{r}
m3 <- glm(y ~ x1 + x2, data = df, family = "binomial")
summary(m3)
```

Call:
glm(formula = y ~ x1 + x2, family = "binomial", data = df)

Deviance Residuals:
    Min      1Q  Median      3Q     Max 
-1.88232 -0.90614 -0.05965  0.86579  2.28489 

Coefficients:
            Estimate Std. Error z value Pr(>|z|)    
(Intercept)  0.9780    0.2945   3.321 0.000897 ***
x1          0.1344    0.1372   0.980 0.327272  
x2         -1.3981    0.2316  -6.035 1.59e-09 *** 
---
Signif. codes:  0 ‘***’ 0.001 ‘**’ 0.01 ‘*’ 0.05 ‘.’ 0.1 ‘ ’ 1

(Dispersion parameter for binomial family taken to be 1)

Null deviance: 277.26 on 199 degrees of freedom
Residual deviance: 209.54 on 197 degrees of freedom
AIC: 215.54

Number of Fisher Scoring iterations: 4
```

The equation of the line (or, in higher dimensions, hyperplane) that forms the decision boundary in logistic regression can be obtained by setting the linear sum of coefficients of this model equal to zero.

$$0.9780 + 0.1344x_1 - 1.3981x_2 = 0$$

$$\implies x_2 = \frac{0.9780 + 0.1344x_1}{1.3981}$$

At any point,  $(x_1, x_2)$ , in the feature space, the model's predicted probability of a positive outcome (i.e. probability of an ER readmission) is related to the coefficients by this equation

$$\log \frac{P[Y = 1]}{1 - P[Y = 1]} = 0.9780 + 0.1344x_1 - 1.3981x_2$$

The decision boundary occurs when  $P[Y = 1] = 0.5$  (total uncertainty, e.g. a

coin toss). Another way to write this equation is:

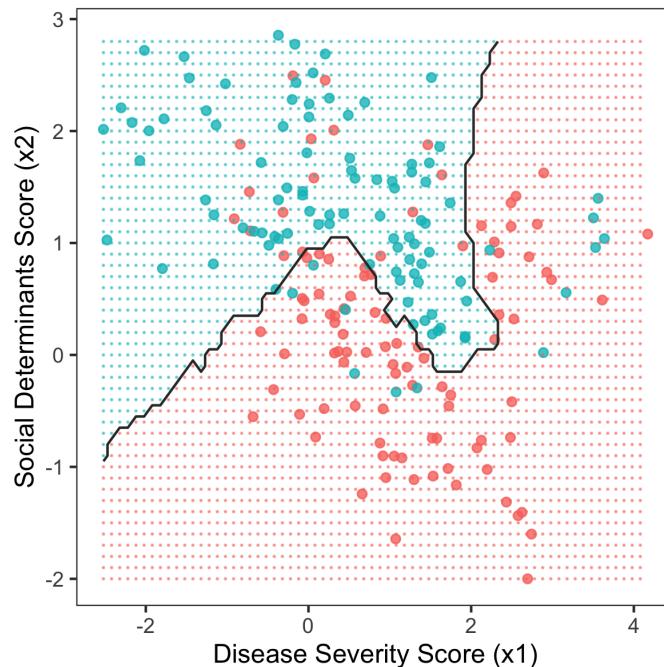
$$P[Y = 1] = \frac{1}{1 + \exp(-(0.9780 + 0.1344x_1 - 1.3981x_2))}$$

The functional form on the right,  $1/(1 + \exp(-z))$ , is called the **logistic function**; this is how logistic regression got its name. We will learn much more about the math behind logistic regression in subsequent chapters.

### 2.3.2 K Nearest Neighbors (KNN)

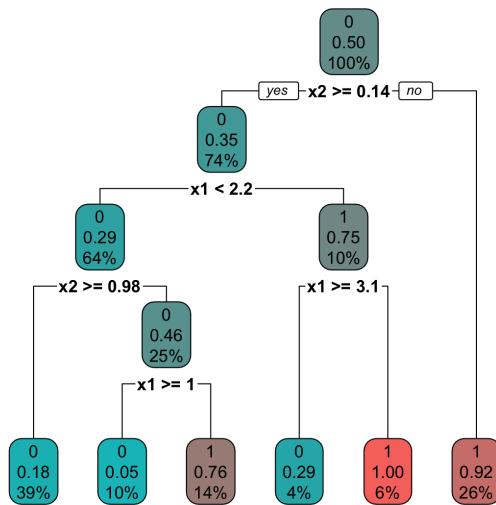
Another – completely different – approach to classification is to start with no assumptions about the shape of the decision boundary. To make a prediction about a new patient, we simply identify the  $K$  nearest neighbors to that patient from our training set and allow them to vote on whether or not the new patient will be readmitted. The parameter  $K$  must be set independently and is called a **hyperparameter**.

Here is the decision boundary for KNN with  $K = 15$ :

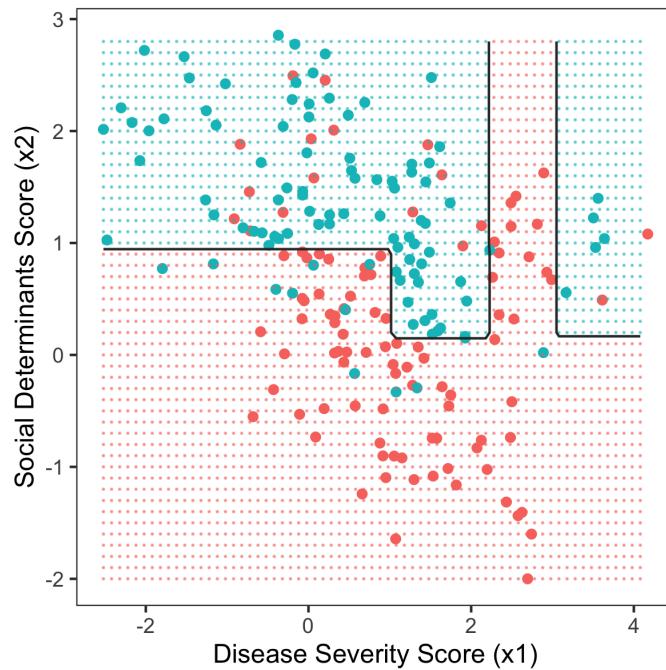


### 2.3.3 Decision Tree

Finally, we may choose to use our training data to build a decision tree, which will allow us to make predictions on new patients using a series of simple yes/no questions. There are different decision tree learning algorithms, but here is the tree produced by a famous one called CART:



And here is the decision boundary produced by this tree:



#### Question 2.1

How can you tell, just by looking at these images, which feature ( $x_1$  or  $x_2$ ) impacts the outcome the most? Which one is it?

#### Question 2.2

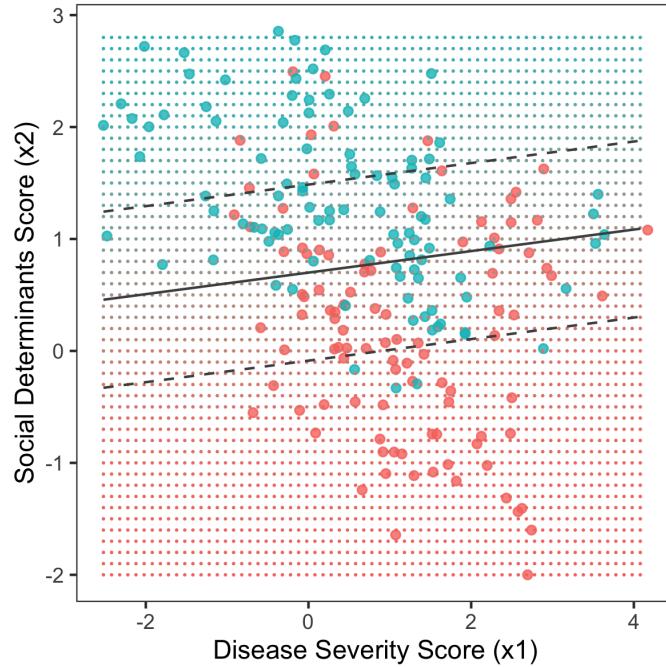
There are six rectangular regions in the picture of the decision tree decision boundary. Each corresponds to one of the six leaves of the tree. Identify all six and which leaves they correspond to on the decision tree.

## 2.4 Classification with Probabilities

We can think of classification as simply drawing a decision boundary, but underlying each algorithm is a quantitative assessment of each point in the feature space. Each algorithm is, in its own way, able to provide a degree of

certainty, or **probability**<sup>2</sup>, that a point belongs to the positive outcome class.

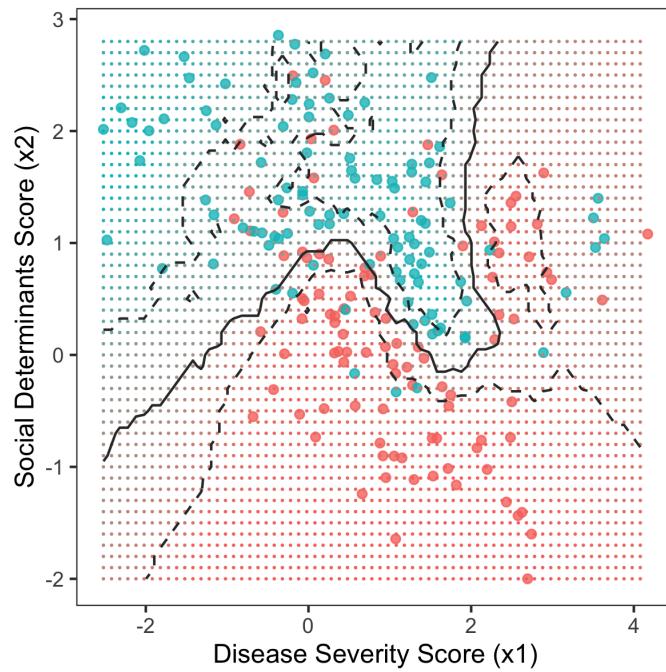
For example, here is the feature space of the example we just saw, colored by the probability, according to logistic regression, that a sample at each point should be classified as positive (i.e. the patient will be readmitted to the ER):



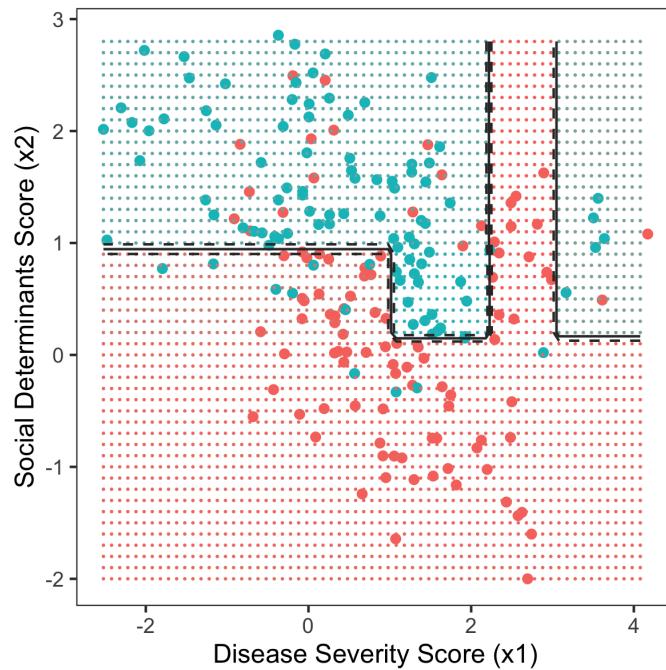
The solid line is the decision boundary, and the dashed lines indicate where the probability of a positive outcome (ER readmission) is 25% (top line) and 75% (bottom line). You can see that the color of the background gets purer red or purer blue the further you get from the decision boundary, but that near the decision boundary, the color is rather murky. That murkiness reflects the algorithm's uncertainty about the outcome. At the decision boundary, it is maximally uncertain. There the probability of a positive outcome is 50%: a coin toss. Here is a similar plot for KNN ( $K = 15$ ):

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<sup>2</sup>Pedantic footnote: this is a Bayesian definition of probability, as opposed to a frequentist definition. More on that later.



You can see that the shapes of the 25% and 75% probability lines have much more complex shapes than for logistic regression, but the story is the same: you have regions of pure blue or red, where the algorithm is certain, and you have a murky region near the decision boundary. Now, finally, here is the same plot for the decision tree:



The color of the background in the regions corresponding to the six leaves of the tree is the same throughout each region. That's because the probability in each rectangular region (corresponding to each leaf of the tree) is constant. It equals the number of red dots in that region divided by the total number of dots.

#### Question 2.3

What are the advantages and disadvantages of each algorithm?

1. Logistic regression?
2. KNN ( $K = 15$ )?
3. Decision tree?

#### Question 2.4

What makes a good classification algorithm? Consider issues of accuracy, generalizability, and speed (both to train the algorithm and to use it to make predictions on new samples).

## Chapter 3

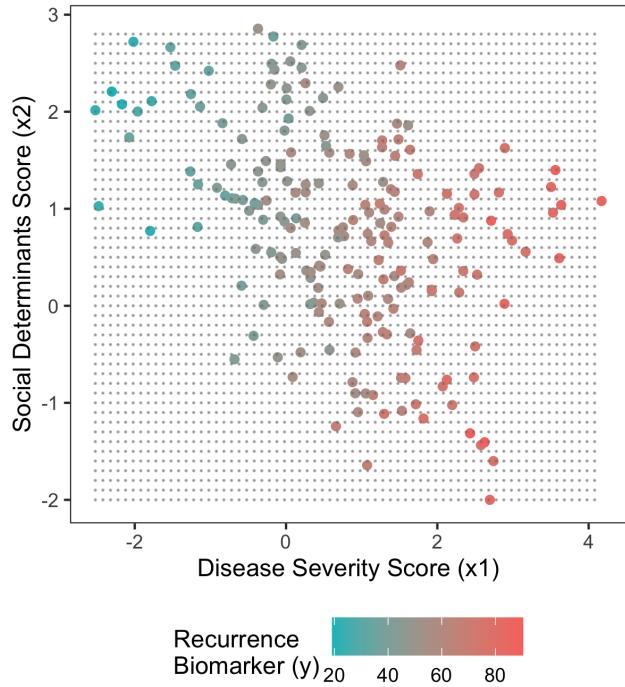
# The Basics of Regression

Classification is a form of supervised learning in which the outcome is a category. **Regression** is another form of supervised learning in which the outcome is a numeric value. For example, it may be a lab value, physical characteristic (height, weight, etc.), or numeric measurement (e.g. oxygen saturation).

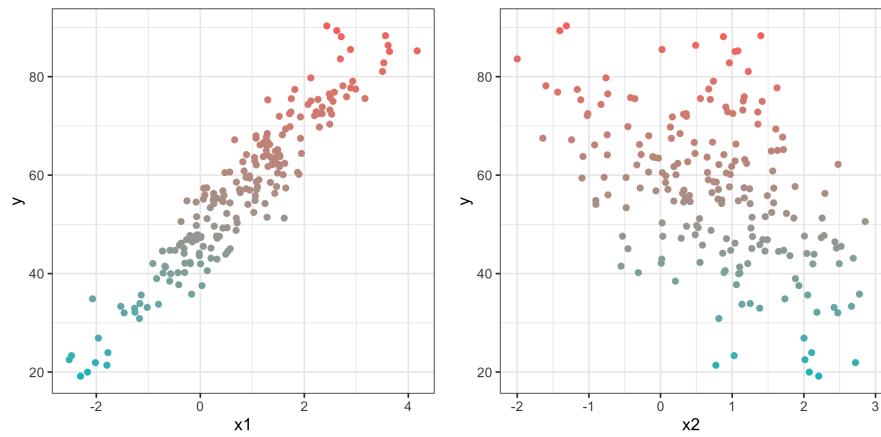
### 3.1 Visualizing the Regression Problem

Let's consider the same setup from Section 2.2 but this time with a quantitative outcome: a "recurrence biomarker" that indicates the likelihood of recurrence of disease.

Again, we have data on two predictors: a disease severity score ( $x_1$ ), which characterizes the severity of the illness for which the patient was originally treated, and a social determinants score ( $x_2$ ), which characterizes a patient's socioeconomic status. We have measurements of  $x_1$  and  $x_2$  on the same 200 patients as in Section 2.2.



This is a plot of the data in a single plane. The color represents the value of the recurrence biomarker – the height of the point above the plane. We want to design a model that will predict the value of the biomarker ( $y$ ) based on the values of the two predictors,  $x_1$  and  $x_2$ . These plots show the **univariate** relationship of each predictor with the outcome.



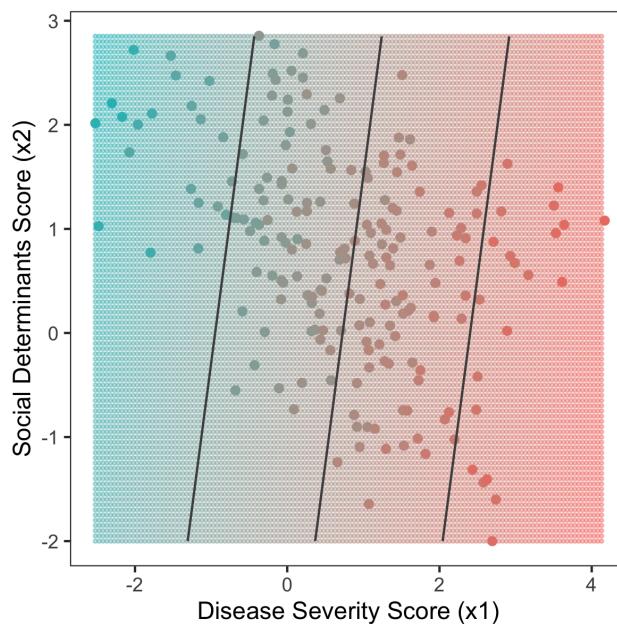
### Question 3.1

Which of the two predictors,  $x_1$  or  $x_2$ , appears to more strongly influence the value of the recurrence biomarker? Explain your reasoning using evidence from the preceding three plots.

## 3.2 Three Regression Algorithms

### 3.2.1 Linear Regression

The regression analogue of logistic regression is **linear regression**<sup>1</sup>. Linear regression creates a hyperplane that slices through the cloud of training data points such that it passes as close as possible, on average, to the data. This is, of course, easiest to see when the feature space is two-dimensional, as it is here:



<sup>1</sup>The terminology here is confusing. When we learn about generalized linear models in Chapter ??, you'll see why logistic regression has the word "regression" in its name even though it's a classification algorithm.

The three lines shown here sit on the hyperplane learned by the linear regression model. They are located at heights corresponding to the 25th, 50th, and 75th percentiles of the outcome,  $y$  (the biomarker value). The plane tilts downward toward the upper left corner of the  $x_1 \times x_2$  grid and upward toward the bottom right corner. It may be helpful to visualize grabbing the  $x_1 \times x_2$  plane and rotating/translating it so that it passes through the middle of the training data. Here is a summary of the trained linear regression model:

```

Call:
lm(formula = y ~ x1 + x2, data = df)

Residuals:
    Min      1Q  Median      3Q     Max 
-11.9218 -3.1032  0.2891  2.8316 12.5813 

Coefficients:
            Estimate Std. Error t value Pr(>|t|)    
(Intercept) 49.8600    0.5370  92.844 < 2e-16 ***
x1          10.4372    0.2855  36.555 < 2e-16 ***
x2         -1.8824    0.3609  -5.215 4.63e-07 ***
---
Signif. codes:  0 ‘***’ 0.001 ‘**’ 0.01 ‘*’ 0.05 ‘.’ 0.1 ‘ ’ 1

Residual standard error: 4.769 on 197 degrees of freedom
Multiple R-squared:  0.9026, Adjusted R-squared:  0.9016 
F-statistic: 912.4 on 2 and 197 DF,  p-value: < 2.2e-16

```

At each point  $(x_1, x_2)$  in the feature space, the model's predicted value of the recurrence biomarker,  $\hat{y}$ , is

$$\hat{y} = 49.8600 + 10.4372x_1 - 1.8824x_2$$

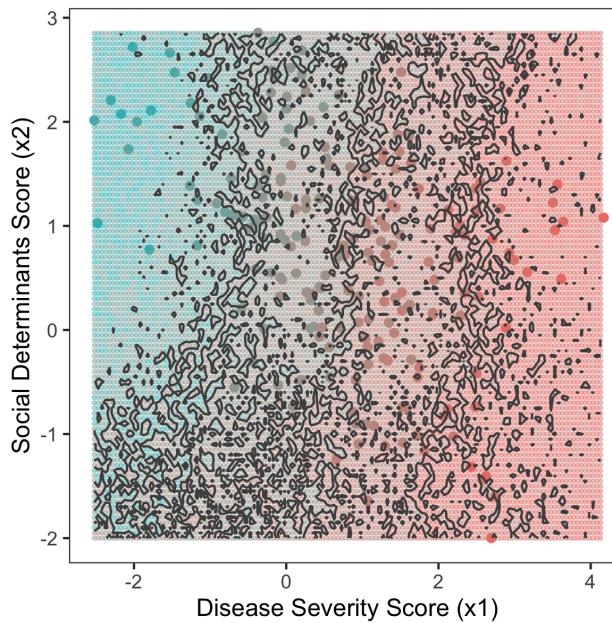
### Question 3.2

Compare and contrast the output from the linear regression model with the output from the logistic regression model in Chapter 2. What looks the same? What looks different? What is being predicted in each case?

### 3.2.2 K Nearest Neighbors (KNN)

Regression using KNN works very similarly to KNN for classification. In classification, we allow the nearest  $K$  points to vote on the label of a new test

point. In regression, we **interpolate** between the values of the surrounding points to come up with the value of  $y$  for a test point. Typically this is done just by averaging the  $y$  values of the nearest  $K$  points, but you can also do something more sophisticated, like weight their contributions by distance to the test point. Here is a contour plot of the regression surface produced by KNN ( $K = 15$ ) for our example:

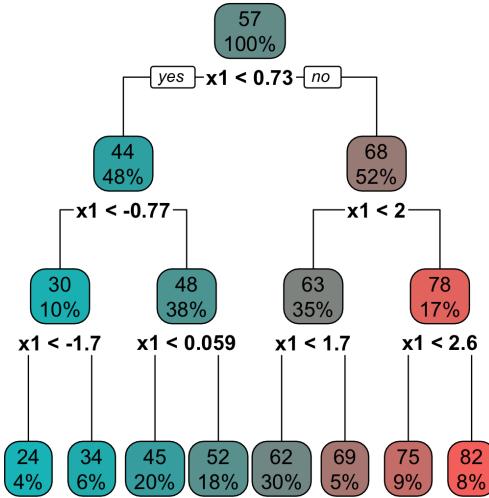


The contours are again drawn at the 25th, 50th, and 75th percentiles of the outcome,  $y$ . This looks like a bit of a mess compared to the linear regression plot, but at the same time, the KNN algorithm is able to capture arbitrarily complex relationships between  $x_1$ ,  $x_2$ , and  $y$  that can be missed by other regression algorithms.

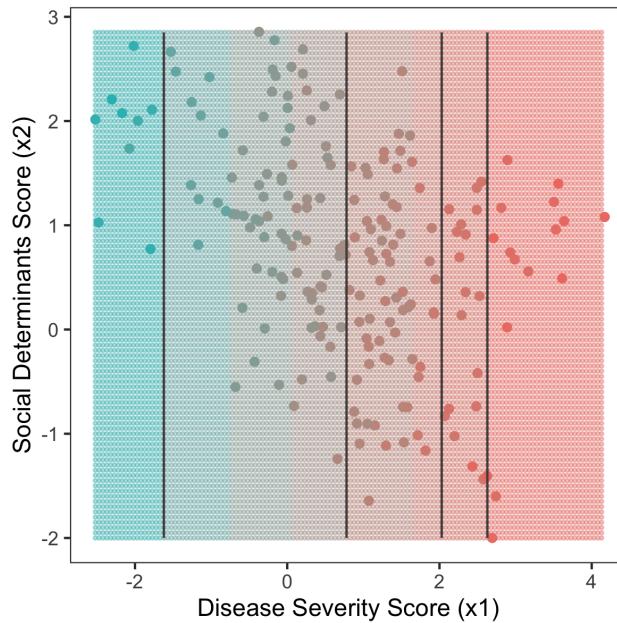
### 3.2.3 Decision Tree

Decision tree regression is similar to decision tree classification except that the output at each leaf is not a class label or the probability of membership in the positive training class (both of which are shown on the tree in Section 2.3.3),

but a numeric value. That value corresponds to the mean outcome value for the points in that leaf.



The predicted biomarker values for a decision tree trained on this dataset (created using the `rpart` package in R with default parameters) are shown here:



You can see that the decision tree always chooses to split on  $x_1$ , the disease severity score, rather than  $x_2$ . Revisit Question 3.1 to remind yourself of why this is. The regression surface produced by the decision tree looks like a set of stairs climbing higher and higher as one moves from left to right across the  $x_1 \times x_2$  plane. The predicted value of  $y$ , the recurrence biomarker, is constant within each stair.

**Question 3.3**

Compare this decision tree with the decision tree for the classification problem in Chapter 2. What is the same? What is different?

**Question 3.4**

This **regression tree** has eight leaves. What region of the feature space does each leaf correspond to?

**Question 3.5**

What are the advantages and disadvantages of each of these three regression algorithms (linear regression, KNN, regression tree)?

## Chapter 4

# Probability Distributions

Many of the methods we will examine in these workshops depend on basic concepts from probability theory. For example, linear and logistic regression are members of a class of supervised learning algorithms called **generalized linear models** (see Chapter ??) which make assumptions about the type of probability distribution followed by the outcome variable. Decision trees use a concept called **entropy** (see Chapter 7), whose mathematical formulation depends on the probability distribution underlying the outcome. Many **hypothesis tests** (see Chapter 6) likewise rely on probabilistic assumptions about the data. Probability is everywhere.

The following sections review some key probability concepts – in an extremely hand-wavey and non-rigorous way – and the properties of some of the most common probability distributions you will encounter in machine learning and statistics.

### 4.1 Definitions

A **probability distribution** is just a mathematical function that provides the relative likelihoods of various possible outcomes of an observation. We call the quantity that is being observed a **random variable**. Probability distributions can be discrete or continuous. The random variable involved can be a number, a vector of numbers, a category/class, etc. The **sample space** is the set of all

possible outcomes. The integral (or sum) of the probability distribution over the entire sample space is 1.0. You will often hear probability distributions for continuous random variables referred to as **probability densities**.

Probability distributions are grouped into families that are characterized by their overall shapes. These families contain **parameters** that, when varied, produce different distributions. Specific probability distributions from within a single family can often look quite different.

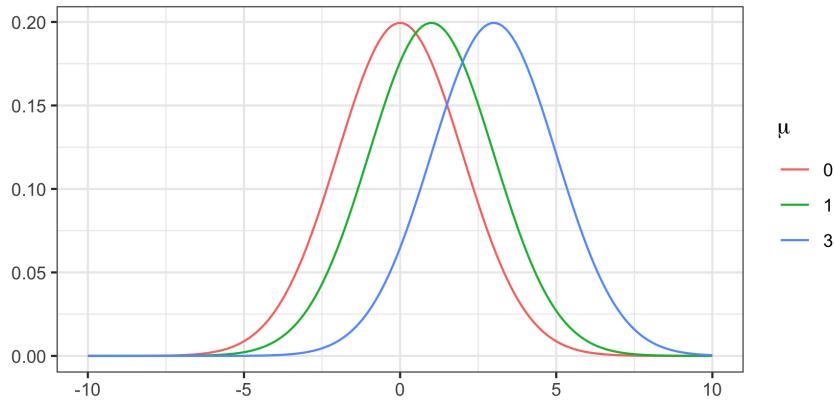
We use the notation  $E[x|\theta]$  to refer to the **expected value**, or mean, of a distribution, given its parameter(s),  $\theta$ . There can be more than one parameter, and it will not always be called  $\theta$ ; this is just an example. We use the notation  $\text{var}(x|\theta)$  to refer to the **variance**, or spread, of a distribution around its mean.

## 4.2 Normal Distribution

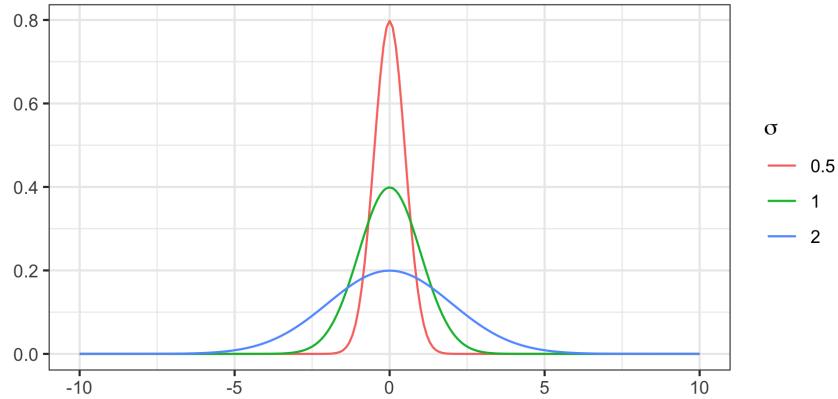
Also called the **Gaussian distribution**, the normal distribution is probably the most well-known continuous probability distribution. It has the following properties:

$$p(x|\mu, \sigma) = \frac{1}{\sqrt{2\pi\sigma^2}} e^{-\frac{(x-\mu)^2}{2\sigma^2}} \quad E[x|\mu, \sigma] = \mu \quad \text{var}(x|\mu, \sigma) = \sigma^2$$

where  $x \in \mathbb{R}$ . We will abbreviate the normal distribution as  $\mathcal{N}(\mu, \sigma)$ . The value of  $\mu$  changes the position of the center of the normal distribution.



The value of  $\sigma$  changes the width of the normal distribution.



#### Question 4.1

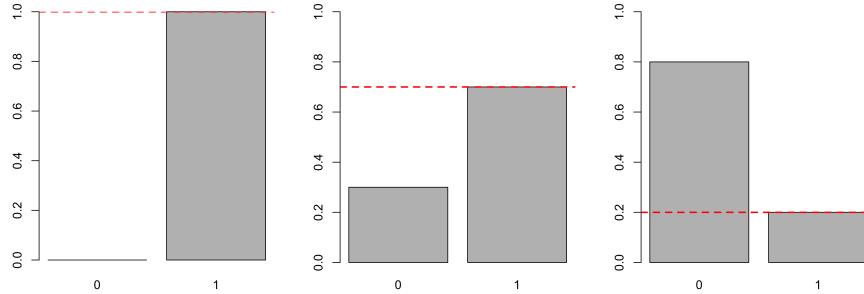
List 5 random variables from medicine or biology that should follow normal distributions.

### 4.3 Bernoulli Distribution

The **Bernoulli distribution** is a discrete probability distribution with the following properties:

$$p(x|\mu) = \mu^x(1-\mu)^{1-x} \quad E[x|\mu] = \mu \quad \text{var}(x|\mu) = \mu(1-\mu)$$

where  $x \in \{0, 1\}$ . It is used to model events where the outcome is yes/no. Think of it as a weighted coin, with  $\mu$  the probability that the coin comes up "heads" on a single toss. Here are three Bernoulli distributions with (from left to right)  $\mu = 1.0, 0.7, 0.2$ . The number along the bottom is  $x$ , which can only be 0 or 1.



The **categorical distribution** is a generalization of the Bernoulli distribution to an outcome with more than two levels. The categorical distribution looks like this:

$$p(x|\phi_1, \dots, \phi_K) = \phi_1^{\mathbb{I}(x=1)} \phi_2^{\mathbb{I}(x=2)} \cdots \phi_K^{\mathbb{I}(x=K)}$$

where  $\sum_{k=1}^K \phi_k = 1$ . The term  $\mathbb{I}(x=j)$  is an **indicator**. It equals 1 if  $x = j$  and 0 otherwise. For example,  $\mathbb{I}(x=2)$  is 1 if  $x = 2$  and 0 otherwise.

#### Question 4.2

List 5 random variables from medicine or biology that should follow Bernoulli distributions.

## 4.4 Binomial Distribution

The **binomial distribution** models the number of positive outcomes,  $x$ , out of  $n$  independent<sup>1</sup> Bernoulli trials, each of which is positive with probability  $\mu$ . This distribution has the following properties, with  $x \in \{0, \dots, n\}$ :

$$p(x|n, \mu) = \binom{n}{x} \mu^x (1 - \mu)^{n-x} \quad E[x|\mu] = n\mu \quad \text{var}(x|\mu) = n\mu(1 - \mu)$$

where the notation  $\binom{n}{x}$  is defined as:

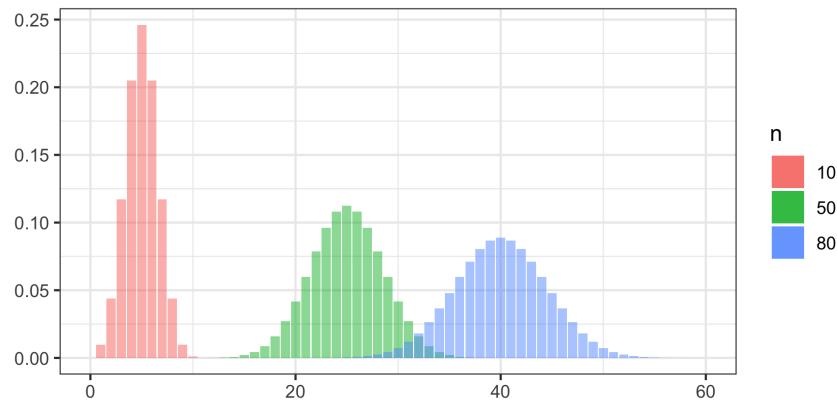
$$\binom{n}{x} = \frac{n!}{x!(n-x)!}.$$

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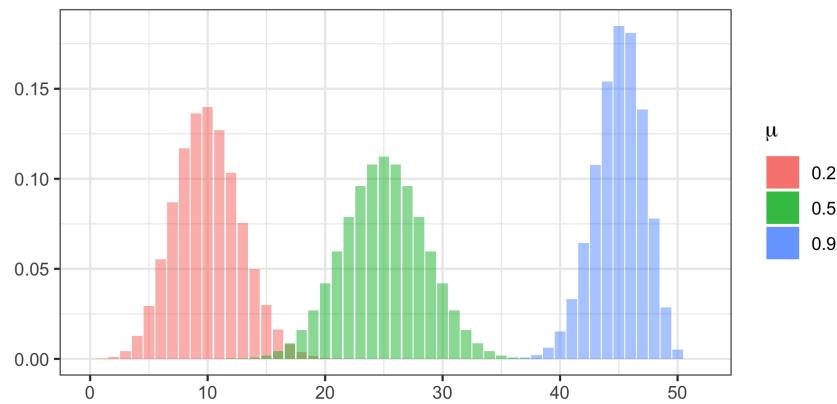
<sup>1</sup>The word **independent** just means that the outcome of one trial does not influence the outcome of any other trial.

This notation denotes the number of ways it is possible to choose  $x$  things out of a group of  $n$  things, where the ordering doesn't matter. The exclamation point denotes the **factorial function**:  $x! = x(x - 1)(x - 2) \cdots (2)(1)$ .

The shape of the binomial distribution is governed by the values of  $n$  and  $\mu$ . Here, we vary  $n$  but keep  $\mu$  constant at 0.5:



And here we vary  $\mu$  but keep  $n$  constant at 50:



#### Question 4.3

List 5 random variables from medicine or biology that should follow binomial distributions.

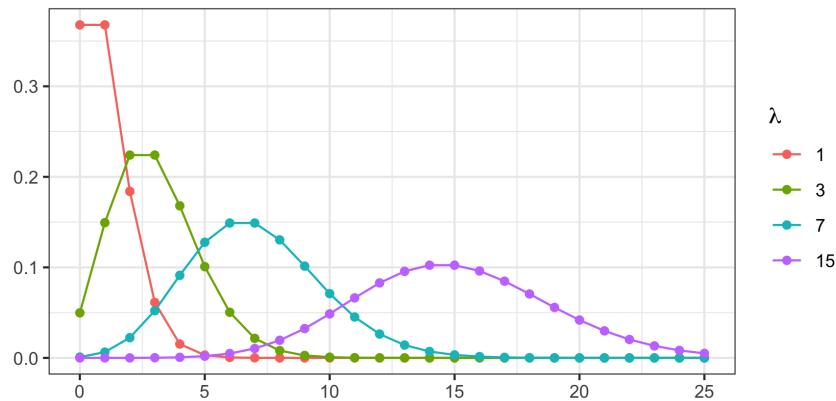
## 4.5 Poisson Distribution

The **Poisson distribution** is a probability distribution that is often used to model discrete quantitative data, such as counts. It has the following properties:

$$p(x|\lambda) = \frac{e^{-\lambda} \lambda^x}{x!} \quad E[x|\lambda] = \lambda \quad \text{var}(x|\lambda) = \lambda$$

where  $x \in \{0, 1, 2, \dots\}$ . Below are four examples of Poisson distributions. If events of a particular type occur continuously and independently at a constant rate (**Poisson process**), the number of events within a time window of fixed width will be distributed according to the Poisson distribution, with rate parameter  $\lambda$  proportional to the width of the window.

Situations where the population size,  $n$ , is large, the probability of an individual event,  $p$ , is small, but the expected number of events,  $np$ , is moderate (say five or more) can generally be modeled using a Poisson distribution with  $\lambda = np$ .



### Question 4.4

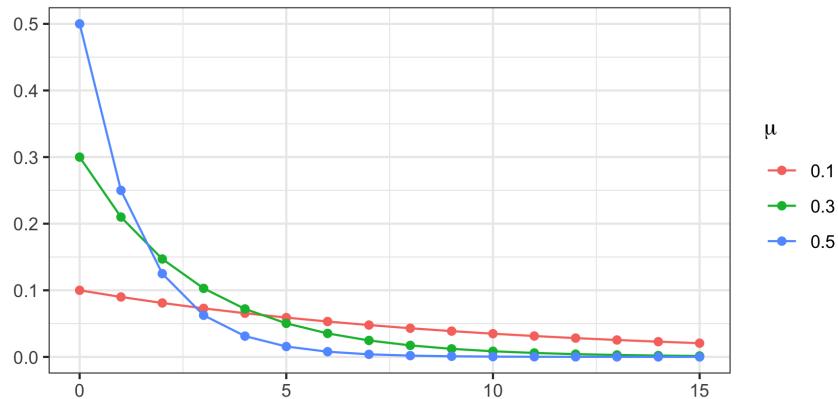
List 5 random variables from medicine or biology that should follow Poisson distributions.

## 4.6 Geometric

The **geometric distribution** models the number of failures in a sequence of Bernoulli trials before the first success. It has the following properties:

$$p(x|\mu) = (1 - \mu)^x \mu \quad E[x|\mu] = \frac{1 - \mu}{\mu} \quad \text{var}(x|\mu) = \frac{1 - \mu}{\mu^2}$$

for  $x \in \{0, 1, 2, \dots\}$ , where  $\mu$  refers to the probability (in the Bernoulli trial) that the trial is a success. Some examples of geometric distributions with different  $\mu$  are shown below:



### Question 4.5

List 5 random variables from medicine or biology that should follow geometric distributions.

## 4.7 Exponential

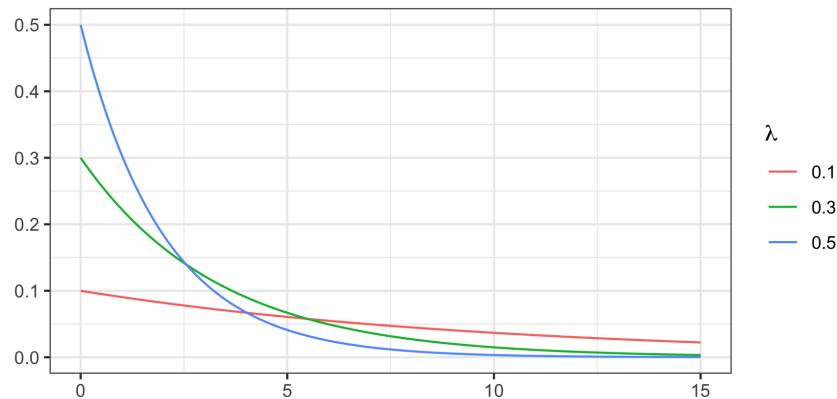
The **exponential distribution** is a continuous probability distribution that models waiting times between events that happen independently and continuously at a constant rate (Poisson process), as well as many other random

variables<sup>2</sup>. It has the following properties:

$$p(x|\lambda) = \lambda e^{-\lambda x} \quad E[x|\lambda] = \frac{1}{\lambda} \quad \text{var}(x|\lambda) = \frac{1}{\lambda^2}$$

where  $x \in \mathbb{R}^+$  ( $x$  is a positive real number, or zero). The exponential distribution is the continuous analogue of the geometric distribution. It is memoryless, which means that the distribution of a waiting time until an event does not depend on how much time has elapsed already.

Here are some different exponential distributions. Compare them to the geometric distribution, above.



#### Question 4.6

List 5 random variables from medicine or biology that should follow exponential distributions.

## 4.8 Chi-Squared Distribution

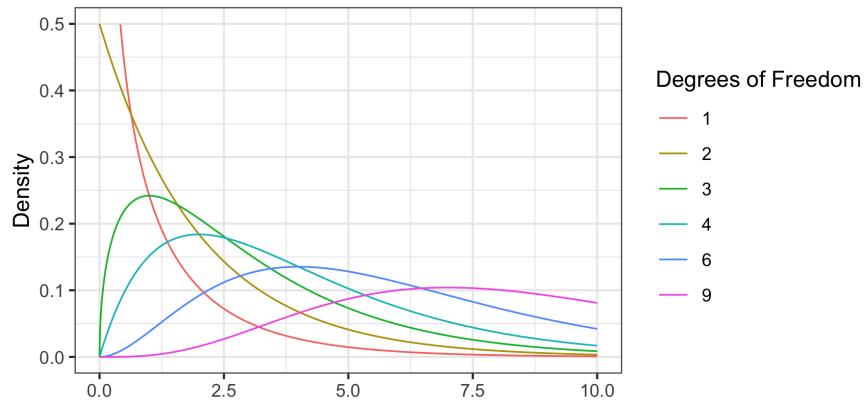
How this distribution arises:

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<sup>2</sup>For example, in an epidemiologic model of an infectious process like COVID-19 community spread, exponential waiting times are often used to model transitions between the susceptible, exposed, infectious, and recovered compartments in the model.

1. If  $Z \sim \mathcal{N}(0, 1)$ , the distribution of  $U = Z^2$  is called the chi-squared distribution with one degree of freedom.
2. If  $U_1, U_2, \dots, U_k$  are independent  $\chi_1^2$  random variables, their sum,  $V = \sum_{i=1}^k U_i$  follows  $\chi_k^2$ , a chi-squared distribution with  $k$  degrees of freedom.

You'll often see the chi-squared distribution used as the sampling distribution for the sample variance in a variety of statistical hypothesis tests. It looks like this:



The parameter  $k$ , the **degrees of freedom**, controls the shape of the chi-squared distribution. The actual formula for the chi-squared distribution looks a bit intimidating, but I'm including it here so you can compare it to the other distributions we've seen:

$$p(x|k) = \frac{1}{2^{k/2}\Gamma(k/2)} x^{k/2-1} e^{-x/2}$$

$$E[x|k] = k \quad \text{var}(x|k) = 2k$$

The gamma function shown in the denominator of the probability density,

$$\Gamma(z) = \int_0^\infty x^{z-1} e^{-x} dx,$$

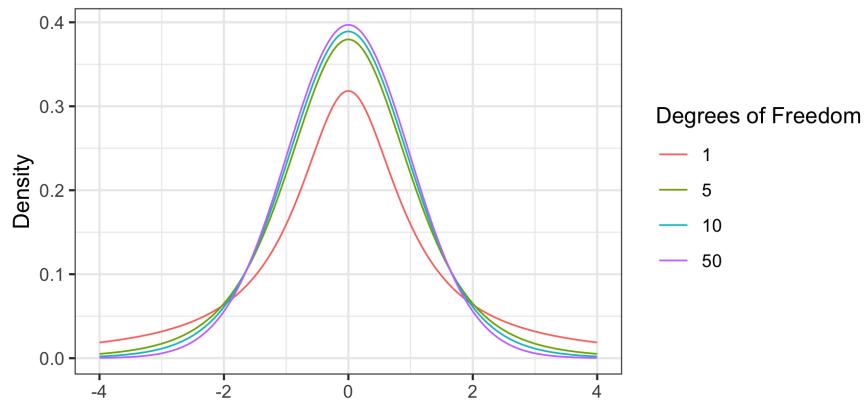
is a generalization of the factorial function to complex numbers. For any positive integer  $n$ ,  $\Gamma(n) = (n-1)!$ .

## 4.9 Student's T Distribution

If  $Z \sim \mathcal{N}(0, 1)$  and  $U \sim \chi_k^2$  and  $Z$  and  $U$  are independent,

$$T = \frac{Z}{\sqrt{U/k}} \sim t_k$$

or in words, the statistic  $T$  follows a  $t$ -distribution with  $k$  degrees of freedom. The T distribution plays an important role in a family of statistical hypothesis tests called T-tests.



Again, the functional form of the T distribution is a bit intimidating, but I'm including it for completeness:

$$p(x|k) = \frac{\Gamma\left(\frac{k+1}{2}\right)}{\sqrt{k\pi} \Gamma\left(\frac{k}{2}\right)} \left(1 + \frac{x^2}{k}\right)^{-\frac{k+1}{2}}$$

$$E[x|k] = 0 \text{ for } k > 1; \text{ otherwise undefined}$$

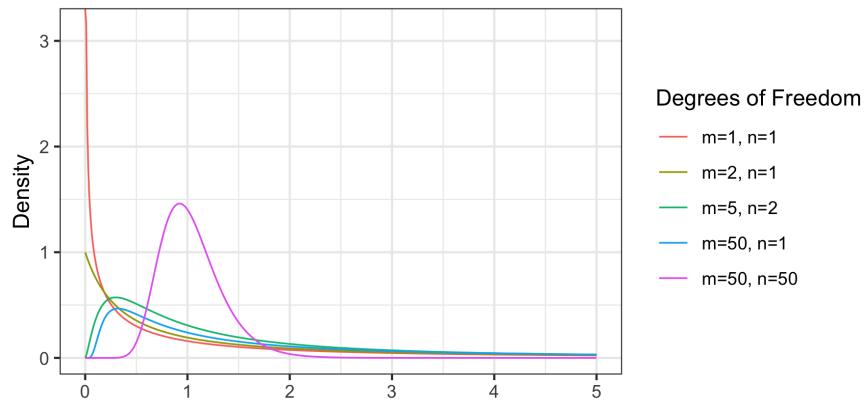
$$\text{var}(x|k) = \begin{cases} \frac{k}{k-2} & k > 2 \\ \infty & 1 < k \leq 2 \\ \text{undefined} & \text{otherwise} \end{cases}$$

## 4.10 F Distribution

If  $U$  and  $V$  are independent  $\chi^2$  random variables with  $m$  and  $n$  degrees of freedom,

$$W = \frac{U/m}{V/n} \sim F_{m,n}$$

or in words, the statistic  $W$  follows an  $F$  distribution with  $m$  and  $n$  degrees of freedom. I'm not writing out the functional form of the  $F$  distribution here because it's too awful-looking, but graphically it looks like this:



Note that if  $T \sim t_k$ , then  $T^2 \sim F_{1,k}$ . The  $F$ -distribution plays an important role in a class of statistical analysis techniques called **ANalysis Of VAriance**, or **ANOVA**.

### Question 4.7

For each of the following experimental conditions, which distribution (from those listed above) provides the best model for how the data  $x^{(1)}, \dots, x^{(n)}$  are generated?

- (a) You are observing several patients' skin in a clinical study to see how long it takes them to develop a rash. You take a picture each day. Let  $x^{(i)}$  be the number of days of *no rash* before the rash occurs.

| Patient ID ( $i$ ) | $x^{(i)}$ |
|--------------------|-----------|
| 1                  | 4         |
| 2                  | 1         |
| 3                  | 0         |
| 4                  | 2         |
| 5                  | 2         |
| 6                  | 4         |
| 7                  | 3         |
| 8                  | 1         |
| 9                  | 0         |
| 10                 | 1         |

- (b) Same situation as above except that instead of taking a picture each day, the patient texts you at the moment he/she observes a rash. The data look like this, where  $x^{(i)}$  is the time (in days) at which patient  $i$  develops a rash:

| Patient ID ( $i$ ) | $x^{(i)}$ |
|--------------------|-----------|
| 1                  | 2.25      |
| 2                  | 3.43      |
| 3                  | 0.68      |
| 4                  | 0.04      |
| 5                  | 3.78      |
| 6                  | 5.65      |
| 7                  | 2.88      |
| 8                  | 3.88      |
| 9                  | 2.83      |
| 10                 | 1.87      |

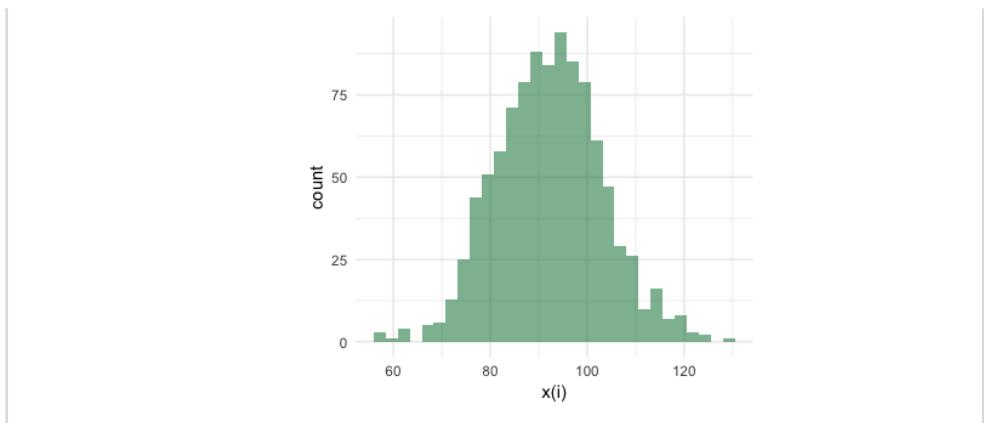
- (c) Imagine you are Ladislaus Bortkiewicz, and you are modeling the number of persons killed by mule or horse kicks in the Prussian army per year. You have data from the late 1800s over the course of 20 years. Let  $x^{(i)}$  be the number of people killed in year  $i$ .

| Year ( $i$ ) | $x^{(i)}$ | Year ( $i$ ) | $x^{(i)}$ |
|--------------|-----------|--------------|-----------|
| 1            | 8         | 11           | 9         |
| 2            | 10        | 12           | 7         |
| 3            | 5         | 13           | 10        |
| 4            | 3         | 14           | 12        |
| 5            | 10        | 15           | 8         |
| 6            | 8         | 16           | 7         |
| 7            | 7         | 17           | 8         |
| 8            | 2         | 18           | 8         |
| 9            | 6         | 19           | 10        |
| 10           | 11        | 20           | 7         |

- (d) Every year, 10 scientists go to the same geographic area (same Lyme prevalence) and they each collect 40 ticks. They test each tick for Lyme disease and record the number of ticks that have Lyme. Let  $x^{(i)}$  be the number of ticks with Lyme in the  $i$ th scientist's bunch.

| Scientist ID ( $i$ ) | $x^{(i)}$ |
|----------------------|-----------|
| 1                    | 8         |
| 2                    | 9         |
| 3                    | 14        |
| 4                    | 15        |
| 5                    | 12        |
| 6                    | 7         |
| 7                    | 6         |
| 8                    | 8         |
| 9                    | 8         |
| 10                   | 14        |

- (e) You have waist circumference data on 1045 men aged 70 and above (see Dey's 2002 paper in the Journal of the American Geriatric Society). It looks like this:



## Chapter 5

# The Basics of Maximum Likelihood Estimation

Beneath our discussions of classification, regression, and probability distributions in Chapters 2, 3, and 4 lies the tricky problem of **model fitting**. We've seen what classification and regression models look like, but we still haven't addressed how to fit these models using training data.

Linear and logistic regression models are fit using a technique called **maximum likelihood (ML) estimation**, in which the model parameters are adjusted to maximize the joint probability of the observed data, or likelihood, given the model.

For example, consider the five different datasets from Question 4.7. In each case, you have some data and an assumption about which probability distribution the data are drawn from. The job of maximum likelihood estimation is to use the data to identify the correct distributional parameters, such as  $\mu$  and  $\sigma$  (in the case of the normal distribution) or  $\lambda$  (in the case of the Poisson distribution). This process is a type of **statistical inference**.

## 5.1 The Likelihood and Log-Likelihood

Let  $p(x|\theta)$  be the probability distribution that governs our data. Here,  $\theta$  stands in for all of the parameters we want to fit.

If we draw independent<sup>1</sup> samples from  $p(x|\theta)$ , the **joint probability density function** for all  $n$  observations is:

$$p(x^{(1)}, x^{(2)}, \dots, x^{(n)}|\theta) = \prod_{i=1}^n p(x^{(i)}|\theta).$$

Since the data are known but the parameter(s)  $\theta$  are unknown, we will view this quantity as a function of  $\theta$ . This is just a change in notation:

$$\mathcal{L}(\theta) = \prod_{i=1}^n p(x^{(i)}|\theta).$$

The higher the joint probability of the data (the more “likely” the data are) given  $\theta$ , the higher the value of this function. We call  $\mathcal{L}(\theta)$  the **likelihood**<sup>2</sup>. Frequently we will want to work with the logarithm of the likelihood, which we call the **log-likelihood**, because it has some nice properties, including allowing us to manipulate sums instead of products<sup>3</sup>:

$$\log \mathcal{L}(\theta) = \sum_{i=1}^n \log p(x^{(i)}|\theta).$$

In maximum likelihood estimation, we seek to find the  $\theta$  for which the likelihood (or log-likelihood) is maximized. We do this by taking derivatives

<sup>1</sup>Independent sampling just means that the values of different samples do not depend on each other. When the samples are drawn independently from the same distribution, their joint probability density is just the product of the individual probability densities (which are all the same).

<sup>2</sup>The distributions we have discussed so far are from a broad family of probability distributions called the **exponential family**. One of the properties of this family is that the log-likelihood is concave. Practically speaking, this means that if we maximize the log-likelihood by setting derivatives equal to zero, we are guaranteed to (a) get only one solution, and (b) find a maximum (not a minimum or an inflection point).

<sup>3</sup>Note that if the function  $f(z)$  has a maximum at  $z'$ , the function  $\log f(z)$  will also have a maximum at  $z'$ , because the logarithmic function is monotonically increasing. So we will get the same parameter estimate(s) either way.

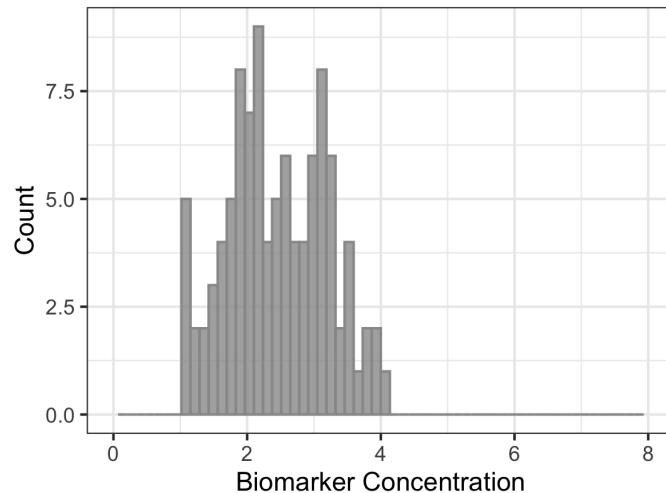
of the log-likelihood with respect to the various parameters and setting them equal to zero. The best-fit parameter estimates obtained in this way are called the **maximum likelihood estimates (MLEs)**.

#### Question 5.1

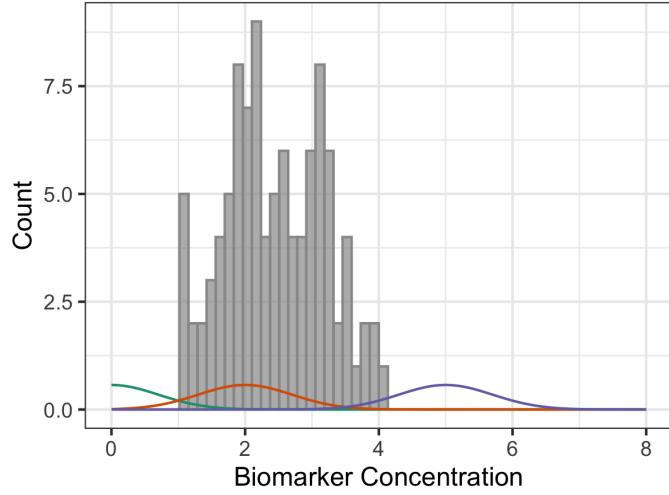
What are some reasons why we might want to fit data to a probability distribution?

## 5.2 Example: Fitting Data to a Normal Distribution

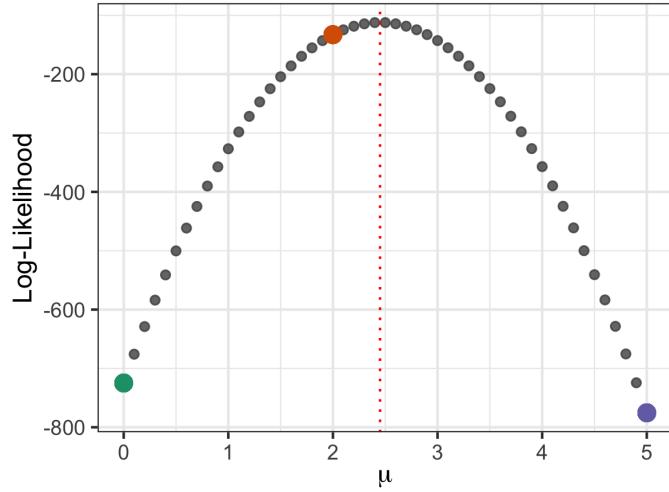
Imagine you have some data from a lab test that measures the concentration of a particular biomarker. You have data from 100 different subjects. A histogram of the raw data looks like this:



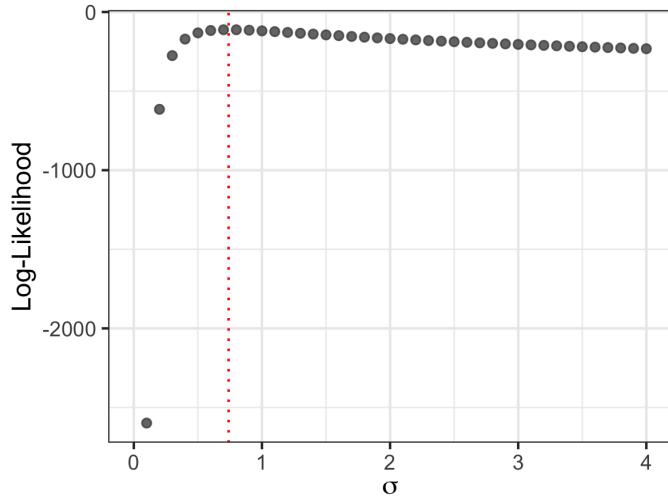
You want to find the normal distribution that best describes these data so you can create a reference distribution for this lab test. To do this, think about trying out several distributions with different values of  $\mu$  and  $\sigma$  and choosing the one that maximizes the log-likelihood. For example, here are three different normal distributions with different values of  $\mu$  and  $\sigma = 0.7$ :



Here is what happens to the log-likelihood as you vary  $\mu$ . The log-likelihoods of the three distributions shown in the plot above are shown as dots with their corresponding colors, and the maximum likelihood estimate is shown as a vertical dotted line.



Now, here's what happens to the log-likelihood when we vary  $\sigma$ , keeping  $\mu$  fixed at its maximum likelihood estimate from the graph above. Again, the maximum likelihood estimate is shown as a vertical dotted line.



For the record, I simulated these data from a normal distribution with  $\mu = 2.5$  and  $\sigma = 0.75$ . The maximum likelihood estimates obtained from this dataset are  $\hat{\mu} = 2.45$  and  $\hat{\sigma} = 0.74$ .

### 5.3 Analytical Calculations of MLEs

In some simple cases, the MLEs can be calculated analytically. We will now go through a bunch of examples of how to find the MLEs of the probability distributions we saw in Chapter 4.

#### 5.3.1 Bernoulli Distribution

The Bernoulli distribution is described in Section 4.3. Our goal is to find the parameter,  $\mu$ , of this distribution, given some observed data,  $x^{(1)}, \dots, x^{(n)}$ . The data will consist of a list of 1s and 0s, since Bernoulli random variables can only take the values 0 or 1.

To find  $\hat{\mu}$ , our MLE for  $\mu$ , we first write down the log-likelihood:

$$\begin{aligned}\log \mathcal{L}(\mu) &= \sum_{i=1}^n \log p(x^{(i)} | \mu) \\ &= \sum_{i=1}^n \log \left( \mu^{x^{(i)}} (1-\mu)^{1-x^{(i)}} \right) \\ &= \sum_{i=1}^n \left[ x^{(i)} \log(\mu) + (1-x^{(i)}) \log(1-\mu) \right]\end{aligned}$$

Then we take the derivative of the log-likelihood with respect to  $\mu$ :

$$\frac{d}{d\mu} \log \mathcal{L}(\mu) = \sum_{i=1}^n \left[ \frac{x^{(i)}}{\mu} - \frac{1-x^{(i)}}{1-\mu} \right]$$

The MLE of  $\mu$  will occur when the likelihood is maximized, which happens when the first derivative equals zero. So to solve for  $\hat{\mu}$ , we set the derivative equal to zero and rearrange:

$$\begin{aligned}\sum_{i=1}^n \left[ \frac{x^{(i)}}{\hat{\mu}} - \frac{1-x^{(i)}}{1-\hat{\mu}} \right] = 0 &\implies (1-\hat{\mu}) \sum_{i=1}^n x^{(i)} = \hat{\mu} \sum_{i=1}^n (1-x^{(i)}) \\ &\implies \boxed{\hat{\mu} = \frac{1}{n} \sum_{i=1}^n x^{(i)}}\end{aligned}$$

We see that the MLE,  $\hat{\mu}$ , is simply the sum of our data – i.e. the number of data points where the outcome is 1 – divided by the total number of observations.

This makes sense: if you want to know the probability that a coin will come up heads, a good way to estimate it is to flip the coin a bunch of times and calculate the fraction of observations in which the coin comes up heads.

### 5.3.2 Binomial Distribution

The binomial distribution is described in Section 4.4. We will make one notational change from that section, which is to call the number of Bernoulli trials  $m$  instead of  $n$ , since we are using  $n$  to refer to the number of data samples. To keep things simple, we will assume that  $m$  is a known quantity.

As before, we first write down the log-likelihood:

$$\begin{aligned}
\log \mathcal{L}(\mu) &= \sum_{i=1}^n \log p(x^{(i)} | m, \mu) \\
&= \sum_{i=1}^n \log \left[ \binom{m}{x} \mu^x (1-\mu)^{m-x} \right] \\
&= \sum_{i=1}^n \left[ \log(m!) - \log(x!) - \log((m-x)!) + x^{(i)} \log(\mu) + (m-x^{(i)}) \log(1-\mu) \right]
\end{aligned}$$

Then we take the derivative of the log-likelihood with respect to  $\mu$ :

$$\frac{d}{d\mu} \log \mathcal{L}(\mu) = \sum_{i=1}^n \left[ \frac{x^{(i)}}{\mu} - \frac{m-x^{(i)}}{1-\mu} \right]$$

We set this equal to zero and solve for  $\hat{\mu}$  (the maximum likelihood estimate of  $\mu$ ):

$$\begin{aligned}
\sum_{i=1}^n \left[ \frac{x^{(i)}}{\hat{\mu}} - \frac{m-x^{(i)}}{1-\hat{\mu}} \right] = 0 \implies (1-\hat{\mu}) \sum_{i=1}^n x^{(i)} = \hat{\mu} \sum_{i=1}^n (m-x^{(i)}) \\
\implies \boxed{\hat{\mu} = \frac{1}{nm} \sum_{i=1}^n x^{(i)}}
\end{aligned}$$

### Question 5.2

Interpret the MLE for the parameter,  $\mu$ , of a binomial distribution, assuming fixed  $m$  (number of trials). Does the MLE for  $\mu$  make intuitive sense to you? Think through a few of your examples from Question 4.3.

### 5.3.3 Normal Distribution

The normal distribution is described in Section 4.2. We will follow the same procedure as in the previous two sections, except that now we have two parameters to solve for,  $\mu$  and  $\sigma$ , instead of one. First, we write down the

log-likelihood:

$$\begin{aligned}
\log \mathcal{L}(\mu, \sigma) &= \sum_{i=1}^n \log p(x^{(i)} | \mu, \sigma) \\
&= \sum_{i=1}^n \log \left( \frac{1}{\sqrt{2\pi\sigma^2}} e^{-\frac{(x^{(i)} - \mu)^2}{2\sigma^2}} \right) \\
&= -\frac{n}{2} \log(2\pi) - \frac{n}{2} \log \sigma^2 - \frac{1}{2\sigma^2} \sum_{i=1}^n (x^{(i)} - \mu)^2
\end{aligned}$$

To find the MLE for  $\mu$ , we take the derivative of the log-likelihood with respect to  $\mu$ :

$$\frac{\partial}{\partial \mu} \log \mathcal{L}(\mu, \sigma) = \frac{1}{\sigma^2} \sum_{i=1}^n (x^{(i)} - \mu)$$

We set this equal to zero and solve for  $\hat{\mu}$  (the maximum likelihood estimate of  $\mu$ ):

$$\frac{1}{\sigma^2} \sum_{i=1}^n (x^{(i)} - \mu) = 0 \implies \boxed{\hat{\mu} = \frac{1}{n} \sum_{i=1}^n x^{(i)}}$$

To find the MLE for  $\sigma$ , we then take the derivative of the log-likelihood with respect to  $\sigma$ :

$$\frac{\partial}{\partial \sigma} \log \mathcal{L}(\mu, \sigma) = -\frac{n}{\sigma} + \frac{1}{\sigma^3} \sum_{i=1}^n (x^{(i)} - \mu)^2$$

We set this equal to zero and solve for  $\hat{\sigma}$  (the maximum likelihood estimate of  $\sigma$ )<sup>4</sup>. Note that the answer depends on our previously calculated MLE for  $\mu$ :

$$-\frac{n}{\hat{\sigma}} + \frac{1}{\hat{\sigma}^3} \sum_{i=1}^n (x^{(i)} - \mu)^2 = 0 \implies \boxed{\hat{\sigma} = \sqrt{\frac{1}{n} \sum_{i=1}^n (x^{(i)} - \hat{\mu})^2}}$$

---

<sup>4</sup>One detail: it turns out this estimate is biased because it depends on the MLE for  $\mu$ . An unbiased version has  $n - 1$  in the denominator instead of  $n$ . The effect of this is minimal unless  $n$  is small.

**Question 5.3**

Interpret the MLEs for the parameters,  $\mu$  and  $\sigma$ , of a normal distribution. Do these results make intuitive sense to you? Think through a few of your examples from Question 4.1.

### 5.3.4 Poisson Distribution

The Poisson distribution is described in Section 4.5. To find the MLE for  $\lambda$ , its mean, we first (as usual) write down the log-likelihood:

$$\begin{aligned}\log \mathcal{L}(\lambda) &= \sum_{i=1}^n \log p(x^{(i)} | \lambda) \\ &= \sum_{i=1}^n \log \left( \frac{e^{-\lambda} \lambda^{x^{(i)}}}{x^{(i)}!} \right) \\ &= \sum_{i=1}^n \left[ -\lambda + x^{(i)} \log(\lambda) - \log(x^{(i)}!) \right]\end{aligned}$$

Now we take the derivative of the log-likelihood with respect to  $\lambda$ :

$$\frac{d}{d\lambda} \log \mathcal{L}(\lambda) = \sum_{i=1}^n \left[ -1 + \frac{x^{(i)}}{\lambda} \right]$$

We set this equal to zero and solve for  $\hat{\lambda}$  (the maximum likelihood estimate of  $\lambda$ ):

$$\sum_{i=1}^n \left[ -1 + \frac{x^{(i)}}{\hat{\lambda}} \right] = 0 \implies \boxed{\hat{\lambda} = \frac{1}{n} \sum_{i=1}^n x^{(i)}}$$

**Question 5.4**

Interpret the MLE for the parameter,  $\lambda$ , of a Poisson distribution. Does this result make intuitive sense to you? Think through a few of your examples from Question 4.4.

### 5.3.5 Geometric Distribution

The geometric distribution is described in Section 4.6. To find the MLE for  $\mu$ , we first write down the log-likelihood:

$$\begin{aligned}\log \mathcal{L}(\mu) &= \sum_{i=1}^n \log p(x^{(i)} | \mu) \\ &= \sum_{i=1}^n \log \left( (1 - \mu)^{x^{(i)}} \mu \right) \\ &= \sum_{i=1}^n \left[ x^{(i)} \log(1 - \mu) + \log(\mu) \right]\end{aligned}$$

Now we take the derivative of the log-likelihood with respect to  $\mu$ :

$$\frac{d}{d\mu} \log \mathcal{L}(\mu) = \sum_{i=1}^n \left[ -\frac{x^{(i)}}{1 - \mu} + \frac{1}{\mu} \right]$$

We set this equal to zero and solve for  $\hat{\mu}$  (the maximum likelihood estimate of  $\mu$ ):

$$\begin{aligned}\sum_{i=1}^n \left[ -\frac{x^{(i)}}{1 - \hat{\mu}} + \frac{1}{\hat{\mu}} \right] &= 0 \implies \frac{n}{\hat{\mu}} = \frac{1}{1 - \hat{\mu}} \sum_{i=1}^n x^{(i)} \\ &\implies \boxed{\hat{\mu} = \frac{n}{\sum_{i=1}^n (x^{(i)} + 1)}}\end{aligned}$$

#### Question 5.5

Interpret the MLE for the parameter,  $\mu$ , of a geometric distribution. Does this result make intuitive sense to you? Think through a few of your examples from Question 4.5.

### 5.3.6 Exponential Distribution

The exponential distribution is described in Section 4.7. To find the MLE for  $\lambda$ , we first write down the log-likelihood:

$$\begin{aligned}\log \mathcal{L}(\lambda) &= \sum_{i=1}^n \log p(x^{(i)}|\lambda) \\ &= \sum_{i=1}^n \log (\lambda e^{-\lambda x^{(i)}}) \\ &= \sum_{i=1}^n [\log(\lambda) - \lambda x^{(i)}]\end{aligned}$$

Now we take the derivative of the log-likelihood with respect to  $\lambda$ :

$$\frac{d}{d\lambda} \log \mathcal{L}(\lambda) = \sum_{i=1}^n \left[ \frac{1}{\lambda} - x^{(i)} \right]$$

We set this equal to zero and solve for  $\hat{\lambda}$  (the maximum likelihood estimate of  $\lambda$ ):

$$\sum_{i=1}^n \left[ \frac{1}{\hat{\lambda}} - x^{(i)} \right] = 0 \implies \boxed{\hat{\lambda} = \frac{n}{\sum_{i=1}^n x^{(i)}}}$$

#### Question 5.6

Interpret the MLE for the parameter,  $\lambda$ , of an exponential distribution. Does this result make intuitive sense to you? Think through a few of your examples from Question 4.6.

## 5.4 Summary of MLEs for Common Distributions

The table below contains a summary of the MLEs of various parameters from some common probability distributions.

| Distribution          | Parameter | ML Estimate                                                             | Domain of $x^{(i)}$  |
|-----------------------|-----------|-------------------------------------------------------------------------|----------------------|
| Univariate Normal     | $\mu$     | $\frac{1}{n} \sum_{i=1}^n x^{(i)}$                                      | $\mathbb{R}$         |
|                       | $\sigma$  | $\frac{1}{n} \sum_{i=1}^n (x^{(i)} - \hat{\mu})^2$                      | $\mathbb{R}$         |
| Multivariate Normal   | $\mu$     | $\frac{1}{n} \sum_{i=1}^n x^{(i)}$                                      | $\mathbb{R}^m$       |
|                       | $\Sigma$  | $\frac{1}{n} \sum_{i=1}^n (x^{(i)} - \hat{\mu})(x^{(i)} - \hat{\mu})^T$ | $\mathbb{R}^m$       |
| Bernoulli             | $\mu$     | $\frac{1}{n} \sum_{i=1}^n x^{(i)}$                                      | $\{0, 1\}$           |
| Binomial (fixed $m$ ) | $\mu$     | $\frac{1}{nm} \sum_{i=1}^n x^{(i)}$                                     | $\{0, 1, \dots, m\}$ |
| Poisson               | $\lambda$ | $\frac{1}{n} \sum_{i=1}^n x^{(i)}$                                      | $\{0, 1, \dots\}$    |
| Geometric             | $\mu$     | $\frac{n}{\sum_{i=1}^n (x^{(i)} + 1)}$                                  | $\{0, 1, \dots\}$    |
| Exponential           | $\lambda$ | $\frac{n}{\sum_{i=1}^n x^{(i)}}$                                        | $\mathbb{R}^+$       |

### Question 5.7

In Question 4.7, we examined several examples of experimental conditions and datasets and discussed which probability distribution best modeled each one. Using the formulas above and the actual datasets from Question 4.7, calculate the MLEs for the parameter(s) of your chosen probability distributions.

## Chapter 6

# Introduction to Hypothesis Testing

Hypothesis testing is a central idea underpinning much of the analysis in the clinical and biomedical research literature<sup>1</sup>. There are multiple approaches to hypothesis testing, but the most common is **null hypothesis testing**, which was developed by the statistician R.A. Fisher. In null hypothesis testing, one creates a model of how the data should look under default conditions and then quantifies the observed data's deviation from that model using a **test statistic**. If the test statistic is large enough, it means there is evidence that the default position is incorrect.

The statisticians Jerzy Neyman and Karl Pearson developed a different approach to hypothesis testing based on the idea of **model comparison**. In their approach, one sets up different models and then quantifies each model's fit to the data; the hypothesis test is used to see whether one model's fit to the data is significantly better than another's. We see the Neyman-Pearson philosophy reflected in techniques such as power calculations and likelihood ratio tests.

Most of the basic hypothesis tests we learn in introductory biostatistics courses (T-tests, chi-squared tests, etc.) follow Fisher's approach. We will

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<sup>1</sup>I should state that there is still a lot of controversy around the whole idea of hypothesis testing and whether *p*-values should be used at all, etc.

focus on null hypothesis testing in this chapter and explore other ideas in subsequent chapters.

## 6.1 Basic Steps of a Hypothesis Test

1. *State the null hypothesis.* The null hypothesis corresponds to the default, or baseline, position; for our example, the null hypothesis might be, “The events ‘has mutation’ and ‘has cancer’ are statistically independent.” The **alternative hypothesis** is the hypothesis that is contrary to the null; for our example, it might be, “The events ‘has mutation’ and ‘has cancer’ are not statistically independent.”
2. *List statistical assumptions.* All hypothesis tests make one or more assumptions about the data, and it’s important to state them clearly. For example, **parametric** hypothesis tests assume the data follow a particular probability distribution under the null, while **nonparametric** tests do not make this assumption.
3. *Decide on an appropriate test and test statistic.* The **test statistic** quantifies the degree of deviation of the observed data from what one would expect under the null hypothesis<sup>2</sup>.
4. *Derive the distribution of the test statistic under the null.* This is called the **null distribution**.
5. *Select a significance level under which you’ll reject the null.* The **significance level**, usually written as  $\alpha$ , is the probability of a type I error. A type I error is committed when one rejects the null even though it is true (false positive result).
6. *Compute the observed value of the test statistic from the data.*
7. *Decide whether or not to reject the null hypothesis.*

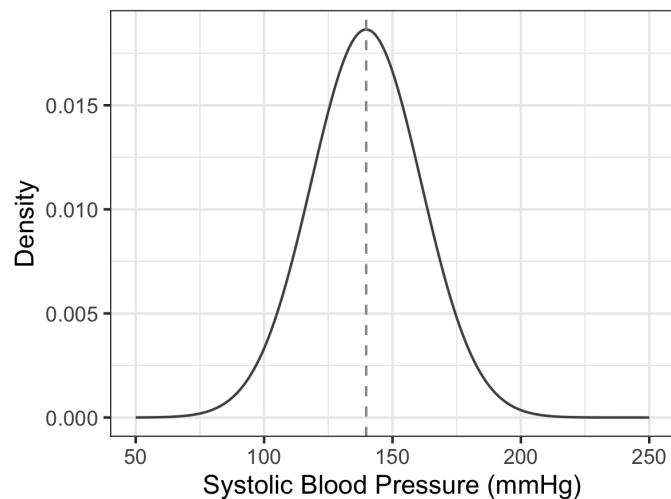
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<sup>2</sup>Some definitions: A **statistic** is just some quantity that summarizes a set of data, or gives some information about the value of a parameter. A **sufficient statistic** is a statistic that gives the maximum amount of information about a parameter that can possibly be obtained from the sample data.

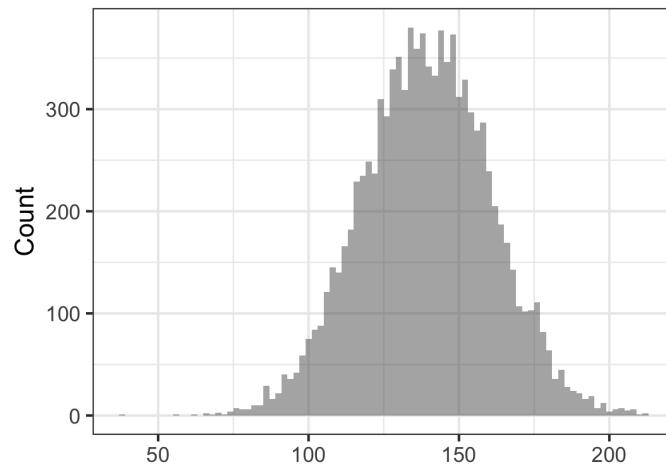
## 6.2 The Z-Test

A **Z-test** is a hypothesis test for which the null distribution is normal with known mean and standard deviation (i.e. known parameters  $\mu$  and  $\sigma$ ). It is most commonly used to compare the mean of a set of samples,  $\bar{x}$ , with a known population mean. It also appears in other contexts, such as significance tests of regression coefficients in generalized linear models (Chapter ??).

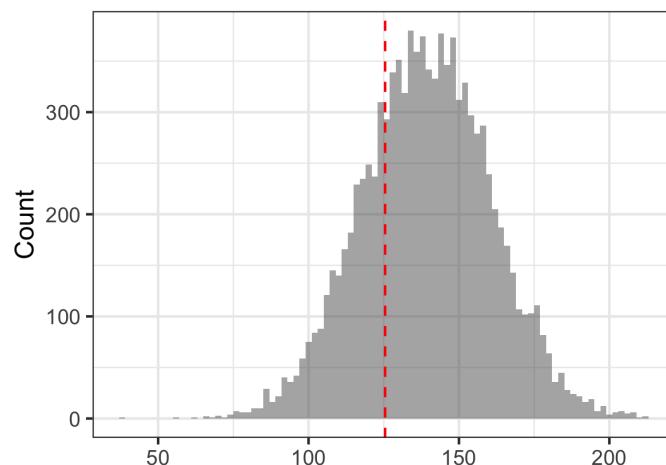
**Example: SBP in an Appalachian Town** The distribution of systolic blood pressure (SBP) among Caucasian males ages 55-64 in the United States is roughly normal with mean 139.75 mmHg and standard deviation 21.40 mmHg (Source: Int. J. Epidemiol. 2: 294-301, 1973). The following graph shows a normal distribution with those parameters.



Here is a histogram of 10,000 data samples drawn independently from that distribution (i.e., what we would expect if we sampled the SBPs of 10,000 men from the United States at large):



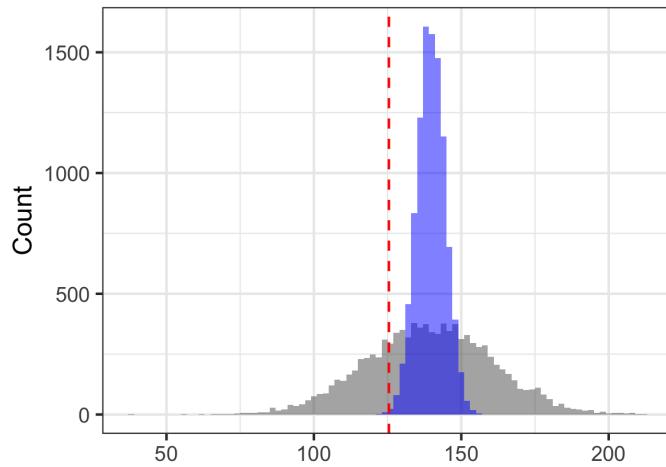
Now, assume some researchers find a small community in rural Appalachia and measure the SBP of 20 Caucasian males ages 55-64 there. Their mean SBP is 125.45 mmHg, illustrated by the red dashed line in the graph below.



At first glance, this may not appear that unusual. After all, the red line is sort of near the center of the gray distribution, right? This analysis is flawed, however, because our 125.45 mmHg value isn't for one man - it's an average

over 20 men. The distribution of the **sample mean**,  $\bar{x}$ , is different from that of each individual sample.

To see this, imagine taking 20 samples from the gray distribution, taking their mean, and recording that value. Now repeat that process 10,000 times. If you do that, you get the **distribution of the sample mean**, which is skinnier than the gray distribution:



It turns out that the distribution of the sample mean will have the same mean,  $\mu_0$ , as the population distribution, but its standard deviation will be  $\sigma / \sqrt{n}$ , where  $n$  is the number of samples over which the mean is taken.

#### Question 6.1

If  $n = 1$ , what is the standard deviation of the sample mean? If  $n = \infty$ , what is the standard deviation of the sample mean?

#### Question 6.2

The sample mean for our 20 sampled Appalachian men is shown as a vertical red dashed line in the figure above. Now that you know what the distribution of the sample mean looks like, do you think the observation from your Appalachian town is “weird”?

Let's conduct a hypothesis test to evaluate whether we have evidence that the mean SBP among men in this town is different from that of the general U.S. population.

1. *State the null hypothesis.* Here the null hypothesis is going to be our default position: that there is no difference. Let  $\mu_c$  be the true mean SBP for men in the community and  $\mu_0$  be the mean for the general population.

$$H_0 : \mu_c = \mu_0$$

$$H_a : \mu_c \neq \mu_0$$

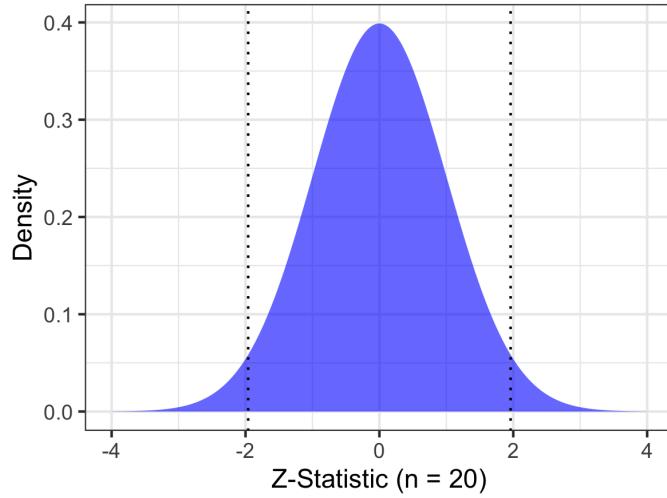
2. *List statistical assumptions.* We make two assumptions. First, we assume that the SBPs of the different men in the sample are statistically independent. Second, we assume that under the null, SBP will follow a normal distribution with mean 139.75 and standard deviation 21.40, the same as the general population of men aged 55-64.
3. *Decide on an appropriate test and test statistic.* Our test statistic in this case is going to be the **Z-statistic**, which measures the deviation of the sample mean from the population mean in units of the standard deviation of the sample mean,  $\sigma / \sqrt{n}$ :

$$Z = \frac{\bar{x} - \mu_0}{\sigma / \sqrt{n}} \quad \text{where} \quad \bar{x} = \frac{1}{n} \sum_{i=1}^n x^{(i)}$$

In our case,  $n = 20$  because  $\bar{x}$ , our sample mean, is an average of 20 samples.

4. *Derive the distribution of the test statistic under the null.* The Z-statistic follows a **standard normal** distribution under the null, which is a normal distribution with  $\mu = 0$  and  $\sigma = 1$ . To see this, remember that the distribution of  $\bar{x}$  under the null is  $\mathcal{N}(\mu_0, \sigma / \sqrt{n})$ . When you calculate the Z-statistic, you shift that distribution by a distance  $\mu_0$  so it is centered at zero, then adjust its width (standard deviation) to 1.0 by dividing by  $\sigma / \sqrt{n}$ .
5. *Select a significance level under which you'll reject the null.* For the purposes of this example, we will choose  $\alpha = 0.05$  (5% chance of a type I error).

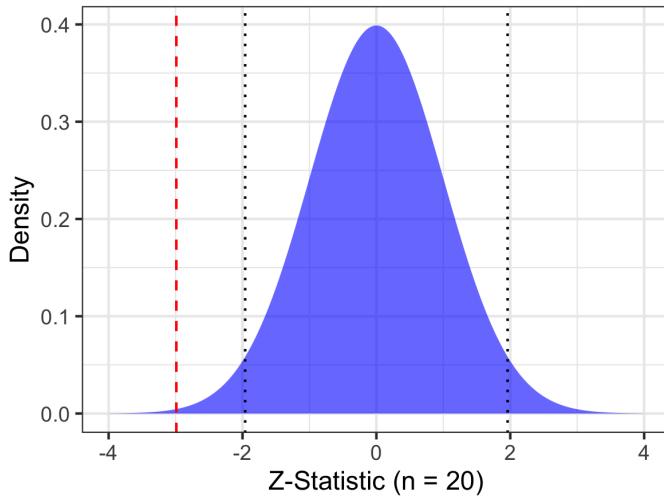
The null distribution of the Z-statistic is shown below. The vertical dotted black lines are situated at the **critical values** that produce  $\alpha = 0.05$  (the area under the null distribution that is outside those lines is 0.05).



6. Compute the observed value of the test statistic from the data. The observed value of the test statistic is:

$$Z = \frac{\bar{x} - \mu_0}{\sigma / \sqrt{n}} = \frac{125.45 - 139.75}{21.40 / \sqrt{20}} = -2.99.$$

7. Decide whether or not to reject the null hypothesis. The value of our test statistic falls outside the region contained by the critical values (the **acceptance region**), so we reject the null at this value of  $\alpha$ .



### Question 6.3

As  $\alpha$  gets smaller, are you more or less likely to reject the null for the same value of the test statistic? Hint: What does making  $\alpha$  smaller do to the positions of the two black dotted lines in the figure, above?

## 6.3 Definitions

- **Type I Error:** When a hypothesis test rejects the null even though the null is true (also called a **false positive**). The type I error rate is usually denoted by  $\alpha$ .
- **Type II Error:** When a hypothesis test fails to reject the null even though it is false (also called a **false negative**). The type II error rate is usually denoted by  $\beta$ .
- **P-value:** The probability of obtaining a test statistic at least as extreme as the one that was actually obtained, assuming the null is true. A *p*-value can be **one-sided** or **two-sided**. The difference lies in the definition of “extreme”. In a one-sided test, we find the probability that the test statistic is at least as extreme *in the same direction* as the one we observed. In a two-sided test, we find the probability that the test statistic is at

least as extreme *in either direction* (positive or negative deviation). In most cases, this has the practical effect of doubling the  $p$ -value.

- **Power:** The probability that a hypothesis test will reject the null when the null is false (that the test will detect a true effect if the effect is there). Usually denoted  $1 - \beta$ .

## 6.4 Pearson's Chi-Squared Test

Imagine you have data on two discrete variables for  $n$  different subjects. You want to test whether the value of one covariate is independent of the value of the other. To do this, you can arrange your data in a **contingency table** where the rows and columns correspond to the values of the two variables. **Pearson's chi-squared test** can then be used to assess the independence of row and column values.

**Example: Association of Genotype and Disease** Imagine you want to test whether a person's genotype at a particular locus is associated with whether or not he/she has Disease X. You find 100 people with the disease and 100 healthy controls ( $n = 200$ ) and genotype them:

|         | AA  | Aa | aa |     |
|---------|-----|----|----|-----|
| X       | 52  | 43 | 5  | 100 |
| Control | 67  | 27 | 6  | 100 |
|         | 119 | 70 | 11 | 200 |

Let's conduct a hypothesis test to examine this result.

1. *State the null hypothesis.* We consider the genotype at this locus,  $G$ , to be a random variable (see Chapter 4) with three possible outcomes:  $AA$ ,  $Aa$ , and  $aa$ . We likewise consider the patient's disease status,  $D$ , to be a

random variable with two possible outcomes: disease or no disease. We state our null hypothesis mathematically as:

$$H_0 : G \perp\!\!\!\perp D$$

$$H_a : G \not\perp\!\!\!\perp D$$

where the symbol  $\perp\!\!\!\perp$  refers to statistical independence of  $G$  and  $D$ . We encountered statistical independence in our discussion of maximum likelihood in Chapter 5. Mathematically, statistical independence means that the joint probability of observing a particular value for  $G$  and a particular value for  $D$  is simply equal to the product of their individual probabilities:

$$P(G = g, D = d) = P(G = g)P(D = d)$$

Under these conditions, the expected values of the cells of our table are:

Under scenario of independence (E):

|         | AA   | Aa   | aa  |     |
|---------|------|------|-----|-----|
| X       | 59.5 | 35.0 | 5.5 | 100 |
| Control | 59.5 | 35.0 | 5.5 | 100 |
|         | 119  | 70   | 11  | 200 |

For example, consider the cell  $G = AA, D = X$ . Assuming the total number of patients is fixed at  $n = 200$  and  $G$  and  $D$  are independent, the expected number of people in that cell is:

$$P(G = AA, D = X) \cdot n = \left(\frac{119}{200}\right) \left(\frac{100}{200}\right) \cdot 200$$

$$= 59.5$$

Our task now is to decide whether our observed table counts are different enough from what we expect under the null to cause us to reject the null.

2. *List statistical assumptions.* We assume that the data are sampled ran-

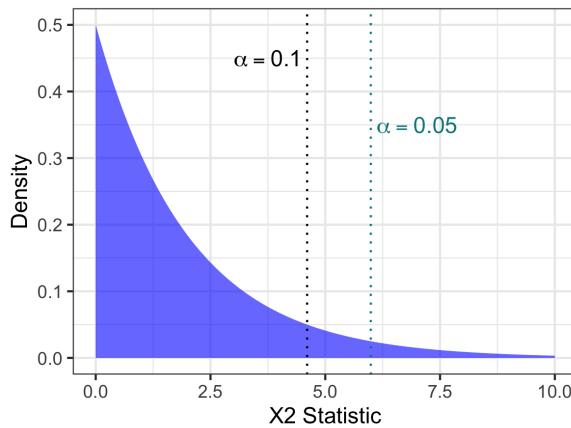
domly and independently from a fixed population where each member of the population has an equal probability of selection<sup>3</sup>.

3. *Decide on an appropriate test and test statistic.* The chi-squared test works by calculating expected counts in all  $r \times c$  cells of the table ( $r$  = number of rows,  $c$  = number of columns) and then measuring the data's deviation from those expected counts. The **chi-squared test statistic** has the form

$$X^2 = \sum_{i=1}^r \sum_{j=1}^c \frac{(O_{ij} - E_{ij})^2}{E_{ij}}$$

where  $O$  refers to "observed count" and  $E$  to "expected count". The expected counts are those that assume statistical independence of rows and columns (blue table, above).

4. *Derive the distribution of the test statistic under the null.* Under the null, the  $X^2$  test statistic follows a chi-squared distribution (Section 4.8) with  $(r - 1)(c - 1)$  degrees of freedom. In the case of our genotype example, there are  $r = 2$  rows and  $c = 3$  columns, thus 2 degrees of freedom.
5. *Select a significance level under which you'll reject the null.* The  $\chi^2$  distribution with 2 degrees of freedom is shown below. Two vertical lines are shown at different significance levels:  $\alpha = 0.05$  and  $\alpha = 0.1$ .



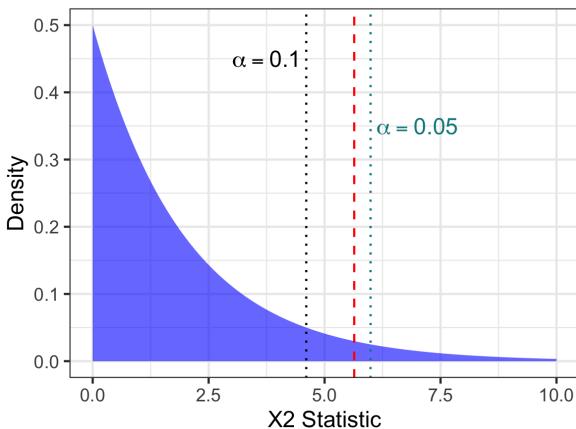

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<sup>3</sup>A further assumption of the chi-squared test is that expected counts for each cell must be sufficiently high. A common rule is 5 or more in all cells of a  $2 \times 2$  table, and 5 or more in 80% of cells in larger tables, but no cells with zero counts.

6. Compute the observed value of the test statistic from the data.

**Question 6.4**

Using the formula in step 4, above, compute the actual value of the chi-squared test statistic for this example. Hint: You should end up with a value that corresponds to the position of the red dashed line in the figure below.



7. Decide whether or not to reject the null hypothesis. Based on our calculated value of the test statistic, we will reject the null at  $\alpha = 0.1$  and fail to reject the null at  $\alpha = 0.05$ .

Although it looks much different from the Z-test, the chi-squared test follows the same formalism: defining a null hypothesis, figuring out what the data should look like under the null, quantifying the deviation of the observed data from what's expected using a test statistic, and deciding if that test statistic presents strong enough evidence to cause us to reject the null.

## 6.5 Student's T-tests

The final example we will look at today is the **T-test**. Like the Z-test, the T-test (actually a family of tests) deals with situations where you have data that are assumed to be normally distributed under the null hypothesis. However, in

this scenario, the population standard deviation,  $\sigma$  is not known and must be estimated from the data itself.

### 6.5.1 One Sample T-test

Assume you have a dataset  $x^{(1)}, \dots, x^{(n)}$ , of real numbers that you can plausibly assume are normally distributed. You want to test whether the mean of your data is equal to a fixed value,  $\mu_0$ . Under the null hypothesis that the means are the same, the test statistic

$$T = \frac{\bar{x} - \mu_0}{s / \sqrt{n}}$$

which we call a “T statistic”, follows a T-distribution (Section 4.9) with  $n - 1$  degrees of freedom<sup>4</sup>. Here  $\bar{x}$  refers to the sample mean, and  $s$  refers to the **sample standard deviation**:

$$s = \sqrt{\frac{1}{n-1} \sum_{i=1}^n (x^{(i)} - \bar{x})^2}$$

#### Question 6.5

Compare the formula for the sample standard deviation to the maximum likelihood estimate of the parameter,  $\sigma$ , of a normal distribution (Section 5.3.3). What is the same/different? Note in particular the use of  $n - 1$  in the denominator, rather than  $n$ . This arises because the MLE for  $\sigma$ ,  $\hat{\sigma}$ , is a **biased** estimate of the population standard deviation (more on this later). For large  $n$ , however, the two are nearly identical.

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<sup>4</sup>A one-sample T-test looks a lot like a Z-test. However, because we use  $s$  to estimate the population standard deviation from data, we must account for variation in our estimate. It turns out that the sample variance,  $s^2$ , follows a chi-squared distribution with  $n - 1$  degrees of freedom, where  $n$  is the sample size. In this case, by the definition of the T-distribution (Section 4.9), the T statistic follows a Student’s T-distribution with  $n - 1$  degrees of freedom. As the number of samples,  $n$ , grows, the sample standard deviation approaches the population standard deviation and the T-test becomes a Z-test. But when  $n$  is small, the T-test is quite a bit more conservative.

### 6.5.2 Two Independent Samples, Equal Variance

Assume you have a dataset  $x^{(1)}, \dots, x^{(n)}$  and another dataset  $y^{(1)}, \dots, y^{(m)}$ . You assume that both are drawn from normal distributions with equal variance but potentially different means. You want to test whether the means are equal.

The same basic machinery for the one-sample T-test can be deployed in this context with a slightly different test statistic. The test statistic

$$T = \frac{\bar{x} - \bar{y}}{s_p \sqrt{\frac{1}{n} + \frac{1}{m}}}$$

where

$$\begin{aligned}s_p^2 &= \frac{(n-1)s_x^2 + (m-1)s_y^2}{m+n-2} \\ s_x^2 &= \frac{1}{n-1} \sum_{i=1}^n (x^{(i)} - \bar{x})^2 \\ s_y^2 &= \frac{1}{m-1} \sum_{i=1}^m (y^{(i)} - \bar{y})^2\end{aligned}$$

follows a  $t$ -distribution with  $m+n-2$  degrees of freedom.

### 6.5.3 Two Independent Samples, Unequal Variance

Sometimes you have two independent samples but cannot assume the variances are equal. Again, similar machinery can be deployed. In this case, you can use **Welch's T-test**, which uses the test statistic

$$T = \frac{\bar{x} - \bar{y}}{s_{xy}}$$

where

$$s_{xy} = \sqrt{\frac{s_x^2}{n} + \frac{s_y^2}{m}}.$$

This test statistic approximately follows a  $t$ -distribution with degrees of freedom given by the Welch-Satterwaite Equation

$$\text{d.f.} = \frac{\left( \frac{s_x^2}{n} + \frac{s_y^2}{m} \right)^2}{\frac{(s_x^2/n)^2}{n-1} + \frac{(s_y^2/m)^2}{m-1}}$$

#### 6.5.4 Matched Pairs

Assume you have a data set of matched pairs. This could be a set of measurements of the same individuals taken at two different points in time, for example, or paired measurements taken from individuals with similar characteristics. You want to test whether the second set of values have changed relative to the first set of values.

To do this, you can use a one-sample T-test on the *differences* of the individual pairs. If no change has occurred, you would expect the mean of those differences to be zero. If we define  $x^{(i)}$  as the difference of the paired observations for sample  $i$  and  $\bar{x}$  as  $\frac{1}{n} \sum_{i=1}^n x^{(i)}$ , the sample mean of those differences, then

$$T = \frac{\bar{x}}{s/\sqrt{n}}$$

follows a T-distribution with  $n - 1$  degrees of freedom.

#### Question 6.6

Here are some sample data. They come from a study that looked at the effect of ozone, a component of smog, on the weight gain of rats. (Original source: Biometrika 63: 421-434, 1976, reproduced in Rice's *Mathematical Statistics and Data Analysis*, p. 465.) A group of 22 seventy-day-old rats were kept in an environment containing ozone for 7 days, and their weight gains were recorded. Another group of 23 rats of a similar age were kept in an ozone-free environment for a similar time and their weight gains were also recorded. Here are the data for the control group:

|    | group   | original_weight | weight_gain |
|----|---------|-----------------|-------------|
| 1  | control | 340.8           | 41.0        |
| 2  | control | 389.1           | 25.9        |
| 3  | control | 355.2           | 13.1        |
| 4  | control | 421.8           | -16.9       |
| 5  | control | 377.1           | 15.4        |
| 6  | control | 404.3           | 22.4        |
| 7  | control | 321.2           | 29.4        |
| 8  | control | 447.5           | 26.0        |
| 9  | control | 305.9           | 38.4        |
| 10 | control | 335.9           | 21.9        |
| 11 | control | 386.3           | 27.3        |
| 12 | control | 377.0           | 17.4        |
| 13 | control | 357.2           | 27.4        |
| 14 | control | 441.7           | 17.7        |
| 15 | control | 383.7           | 21.4        |
| 16 | control | 373.7           | 26.6        |
| 17 | control | 336.0           | 24.9        |
| 18 | control | 419.4           | 18.3        |
| 19 | control | 287.1           | 28.5        |
| 20 | control | 602.8           | 21.8        |
| 21 | control | 325.4           | 19.2        |
| 22 | control | 452.4           | 26.0        |
| 23 | control | 398.9           | 22.7        |
|    | Mean    | control         | 384.4       |
|    | St.Dev. | control         | 65.5        |
|    |         |                 | 10.8        |

And here are the data for the ozone group:

|         | group | original_weight | weight_gain |
|---------|-------|-----------------|-------------|
| 1       | ozone | 437.4           | 10.1        |
| 2       | ozone | 275.9           | 7.3         |
| 3       | ozone | 296.3           | -9.9        |
| 4       | ozone | 295.9           | 17.9        |
| 5       | ozone | 379.7           | 6.6         |
| 6       | ozone | 274.1           | 39.9        |
| 7       | ozone | 360.0           | -14.7       |
| 8       | ozone | 331.9           | -9.0        |
| 9       | ozone | 531.8           | 6.1         |
| 10      | ozone | 350.5           | 14.3        |
| 11      | ozone | 345.7           | 6.8         |
| 12      | ozone | 268.1           | -12.9       |
| 13      | ozone | 339.9           | 12.1        |
| 14      | ozone | 352.4           | -15.9       |
| 15      | ozone | 435.8           | 44.1        |
| 16      | ozone | 476.9           | 20.4        |
| 17      | ozone | 462.5           | 15.5        |
| 18      | ozone | 368.0           | 28.2        |
| 19      | ozone | 504.3           | 14.0        |
| 20      | ozone | 188.0           | 15.7        |
| 21      | ozone | 466.9           | 54.6        |
| 22      | ozone | 288.8           | -9.0        |
| Mean    | ozone | 365.0           | 11.0        |
| St.Dev. | ozone | 88.6            | 19.0        |

- (a) Imagine that the population weight distribution of rats is known to be normal with  $\mu = 350$  (grams) and unknown  $\sigma$ . How would you test the hypothesis that the mean of the control group is equal to the population mean? How would you test the hypothesis that the mean of the ozone group is equal to the population mean?
- (b) How would you test the hypothesis that the mean original weights of the ozone and control groups are equal? Do not assume equal variance.
- (c) How would you test the hypothesis that the mean weight gain in the ozone group is equal to the mean weight gain in the control group? Do not assume equal variance.
- (d) How would your approach in part (c) change if you assumed the weight gains in the two groups had equal variance?

Plug in the relevant numbers from the tables above to perform each hypothesis test with  $\alpha = 0.05$ . The following table of critical values for the  $T$ -distribution<sup>a</sup> may help you:

Critical Values for Student's  $t$ -Distribution.

| df | Upper Tail Probability: $\Pr(T > t)$ |       |       |       |        |        |        |        |        |         |
|----|--------------------------------------|-------|-------|-------|--------|--------|--------|--------|--------|---------|
|    | 0.2                                  | 0.1   | 0.05  | 0.04  | 0.03   | 0.025  | 0.02   | 0.01   | 0.005  | 0.0005  |
| 1  | 1.376                                | 3.078 | 6.314 | 7.916 | 10.579 | 12.706 | 15.895 | 31.821 | 63.657 | 636.619 |
| 2  | 1.061                                | 1.886 | 2.920 | 3.320 | 3.896  | 4.303  | 4.849  | 6.965  | 9.925  | 31.599  |
| 3  | 0.978                                | 1.638 | 2.353 | 2.605 | 2.951  | 3.182  | 3.482  | 4.541  | 5.841  | 12.924  |
| 4  | 0.941                                | 1.533 | 2.132 | 2.333 | 2.601  | 2.776  | 2.999  | 3.747  | 4.604  | 8.610   |
| 5  | 0.920                                | 1.476 | 2.015 | 2.191 | 2.422  | 2.571  | 2.757  | 3.365  | 4.032  | 6.869   |
| 6  | 0.906                                | 1.440 | 1.943 | 2.104 | 2.313  | 2.447  | 2.612  | 3.143  | 3.707  | 5.959   |
| 7  | 0.896                                | 1.415 | 1.895 | 2.046 | 2.241  | 2.365  | 2.517  | 2.998  | 3.499  | 5.408   |
| 8  | 0.889                                | 1.397 | 1.860 | 2.004 | 2.189  | 2.306  | 2.449  | 2.896  | 3.355  | 5.041   |
| 9  | 0.883                                | 1.383 | 1.833 | 1.973 | 2.150  | 2.262  | 2.398  | 2.821  | 3.250  | 4.781   |
| 10 | 0.879                                | 1.372 | 1.812 | 1.948 | 2.120  | 2.228  | 2.359  | 2.764  | 3.169  | 4.587   |
| 11 | 0.876                                | 1.363 | 1.796 | 1.928 | 2.096  | 2.201  | 2.328  | 2.718  | 3.106  | 4.437   |
| 12 | 0.873                                | 1.356 | 1.782 | 1.912 | 2.076  | 2.179  | 2.303  | 2.681  | 3.055  | 4.318   |
| 13 | 0.870                                | 1.350 | 1.771 | 1.899 | 2.060  | 2.160  | 2.282  | 2.650  | 3.012  | 4.221   |
| 14 | 0.868                                | 1.345 | 1.761 | 1.887 | 2.046  | 2.145  | 2.264  | 2.624  | 2.977  | 4.140   |
| 15 | 0.866                                | 1.341 | 1.753 | 1.878 | 2.034  | 2.131  | 2.249  | 2.602  | 2.947  | 4.073   |
| 16 | 0.865                                | 1.337 | 1.746 | 1.869 | 2.024  | 2.120  | 2.235  | 2.583  | 2.921  | 4.015   |
| 17 | 0.863                                | 1.333 | 1.740 | 1.862 | 2.015  | 2.110  | 2.224  | 2.567  | 2.898  | 3.965   |
| 18 | 0.862                                | 1.330 | 1.734 | 1.855 | 2.007  | 2.101  | 2.214  | 2.552  | 2.878  | 3.922   |
| 19 | 0.861                                | 1.328 | 1.729 | 1.850 | 2.000  | 2.093  | 2.205  | 2.539  | 2.861  | 3.883   |
| 20 | 0.860                                | 1.325 | 1.725 | 1.844 | 1.994  | 2.086  | 2.197  | 2.528  | 2.845  | 3.850   |
| 21 | 0.859                                | 1.323 | 1.721 | 1.840 | 1.988  | 2.080  | 2.189  | 2.518  | 2.831  | 3.819   |
| 22 | 0.858                                | 1.321 | 1.717 | 1.835 | 1.983  | 2.074  | 2.183  | 2.508  | 2.819  | 3.792   |
| 23 | 0.858                                | 1.319 | 1.714 | 1.832 | 1.978  | 2.069  | 2.177  | 2.500  | 2.807  | 3.768   |

**Answers:** (a) One-sample  $T$ -test of control group original weights vs. null of  $\mu_0 = 350$ ;  $T$ -statistic is 2.5165, 22 d.f., two-sided  $p$ -value is 0.01964, reject null at  $\alpha = 0.05$ . One-sample  $T$ -test of ozone group original weights vs. null of  $\mu_0 = 350$ ;  $T$ -statistic is 0.7961, 21 d.f., two-sided  $p$ -value is 0.4349, fail to reject null at  $\alpha = 0.05$ . (b) Welch's two-sample  $T$ -test of control vs. ozone group original weights;  $T$ -statistic is 0.8293, d.f. is estimated using the Welch-Satterwaite equation at 38.619, two-sided  $p$ -value is 0.4120, fail to reject null at  $\alpha = 0.05$ . (c) Welch's two-sample  $T$ -test of control vs. ozone group weight gains;  $T$ -statistic is 2.4629, d.f. is estimated using the Welch-Satterwaite equation at 32.918, two-sided  $p$ -value is 0.01918, reject null at  $\alpha = 0.05$ . (d) You would use Pearson's two-sample  $T$ -test, which assumes equal variances;  $T$ -statistic is 2.4919, d.f. is 43, two-sided  $p$ -value is 0.01664, reject null at  $\alpha = 0.05$ .

<sup>a</sup>Borrowed with gratitude from <https://www.stat.purdue.edu/lfindsen/stat503/t-Dist.pdf>

# Chapter 7

## Building a Decision Tree

**Decision trees** were developed as an alternative to neural networks in the 1970s. They can be used either for classification or regression. We already saw them in Chapters 2 and 3 as examples of supervised learning algorithms. Now we're going to get into a bit more detail about how these trees are learned from data.

There are several algorithms for fitting decision trees. All of them are **greedy** and are not guaranteed to give the optimal solution.

### 7.1 Understanding the Problem

### 7.2 Tree Learning Algorithms

### 7.3 Regression Trees

#### 7.3.1 Entropy and Information Gain

Today we will discuss the ID3 algorithm for building decision trees, which relies on the concepts of entropy and information gain. **Entropy**, usually abbreviated  $H$ , is a measure of the uncertainty in the value of a random variable. It is the number of bits (on average) required to describe the outcome

of the random variable. Here is the formula for the entropy of the discrete probability distribution governing the outcome of a random variable,  $X$ :

$$H(X) = - \sum_x P(X = x) \log_2 (P(X = x))$$

For a Bernoulli random variable, there are only two possible outcomes: 0 and 1. The entropy of this random variable is given by:

$$H_{\text{Bernoulli}} = -\mu \log_2(\mu) - (1 - \mu) \log_2(1 - \mu)$$

where  $\mu$ , as usual, is the probability the outcome is 1.

Let  $Y$  be the outcome variable of a training set. Let  $X$  be some other random variable defined over the training set. It could be one of the original predictors or some arbitrary combination of them. **Information gain** is defined as:

$$\begin{aligned} \text{Gain}(Y, X) &= H(Y) - \sum_x P(X = x) H(Y|X = x) \\ &= H(Y) - H(Y|X) \end{aligned}$$

It is a measure of how much our uncertainty in the value of  $Y$  is reduced by knowing  $X$ .

### 7.3.2 The ID3 Algorithm

Here is the algorithm:

1. Start with a single node representing the entire dataset.
2. At each current leaf node in the tree:
  - (a) Compute the information gain for each feature in turn.
  - (b) Split on the one with the highest information gain.
3. Return to Step 2. Stop the recursion when either the class distributions at the leaf nodes are entirely pure (all data points at a leaf have the same outcome class), or there are no more variables left to split on.

### 7.3.3 Decision Tree Regression

So far we've assumed that our outcome is discrete. But what happens if it's numeric? (That is, what if we want to perform regression instead of classification?)

In that case, we use **standard deviation reduction** instead of information gain to decide which variables to split on. The sample standard deviation of an outcome,  $y$ , is defined as:

$$S(Y) = \sqrt{\frac{\sum_i (y^{(i)} - \bar{y})^2}{n - 1}}$$

The procedure is identical to the ID3 algorithm except you use conditional standard deviation instead of information gain to decide on features. We define

$$S(Y, X) = \sum_x P(X = x) S(Y|X = x)$$

and at each current leaf node, we split on the variable where the reduction in standard deviation,  $S(Y) - S(Y, X)$ , is the highest.

### 7.3.4 Numeric Predictors

So far we've also assumed that our predictors are discrete. But decision trees can handle numeric predictors as well. There are many different strategies for deciding on an optimal split for a predictor. Two simple ones:

- Split at the median or mean of the predictor.
- Order the datapoints on the value of the predictor and consider each possible split, looking for the one that gives the greatest information gain/standard deviation reduction. So for example, if you have a predictor called "age" and its values are 10, 11, 16, 18, 20, and 35, consider all  $N - 1 = 5$  possible split points. (This is the approach used by C4.5, a successor to ID3.)

If you have a large dataset, the second option is probably not practical, but you can downsample your dataset first and then look for the optimal cut point(s).

What if the outcome is numeric? In that case, we can use **standard deviation reduction** instead of information gain to decide which variables to split on. The sample standard deviation of an outcome,  $y$ , is defined as:

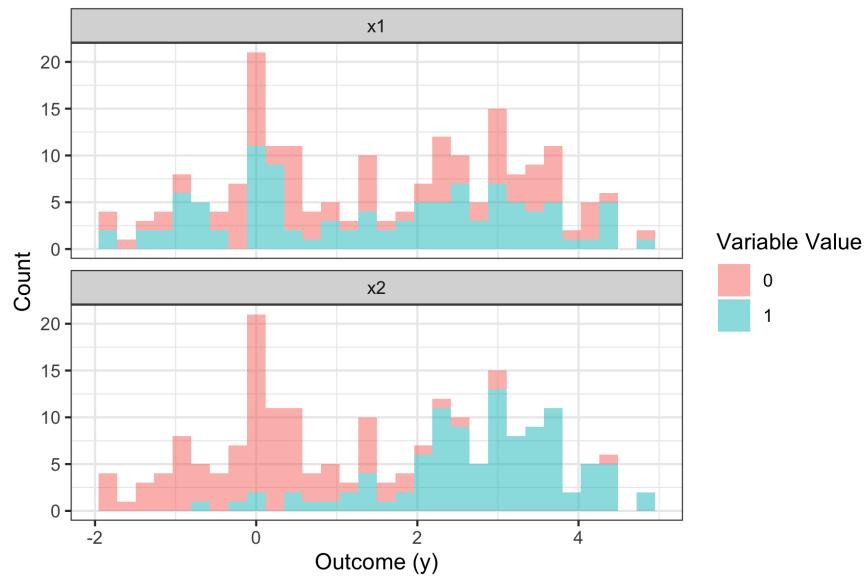
$$S(Y) = \sqrt{\frac{\sum_i (y^{(i)} - \bar{y})^2}{n - 1}}$$

where  $\bar{y}$  is the overall mean of the outcome. The procedure is identical to the ID3 algorithm (see Chapter 7) except you use conditional standard deviation instead of information gain to decide on features. We define

$$S(Y, X) = \sum_{x \in \text{Values}(X)} \frac{|Y(X = x)|}{|Y|} S(Y(X = x))$$

and at each current leaf node, we split on the variable where the reduction in standard deviation,  $S(Y) - S(Y, X)$ , is the highest.

For example, imagine you had a dataset similar in structure to our example, but instead of two real-valued predictors, you have two binary predictors,  $x_1$  and  $x_2$ . The decision tree algorithm could choose either one of them to split on first. Here are the distributions of outcome values associated with  $x_1$  and  $x_2$ .



### Question 7.1

Which of these two variables,  $x_1$  or  $x_2$ , would make the most sense for a decision tree to split on? What would such a split look like and what would the output value of the tree (the predicted value of  $y$ ) be for each side of the split?

## **Chapter 8**

# **The Perils of Time-to-Event Outcomes**

## **Chapter 9**

# **The Kaplan-Meier Curve**