Review of Probability and Statistics

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STAT 540

Preview of next 6 lectures

- **Lecture 4: Review of Probability and Statistics**
- Lecture 5: Statistical Inference - two group comparisons
- Lecture 6: Statistical Inference - linear regression and ANOVA
- Lecture 7: Statistical Inference - multiple linear regression
- Lecture 8: Statistical Inference - continuous regression + limma
- Lecture 9: Statistical Inference - multiple testing

What is Statistics?

- The field of statistics concerns the science of **collecting, analyzing/modeling, interpreting** data and **communicating uncertainty** about the results

- Statistics is **not** a collection of generic “recipes” to follow

- Data science and machine learning have facilitated application to ‘big data’

- Our (statistical) goals for this course:
  - gain a rigorous understanding of core principles of common analyses of high-dimensional biological data
  - build solid foundation to follow up on specific topics

Today: review terminology and basic concepts

- The relationship between statistical inference and probability
- Random variables and their probability distributions
- Models, parameters, and their estimators
- Central Limit Theorem (CLT)
- Hypothesis testing

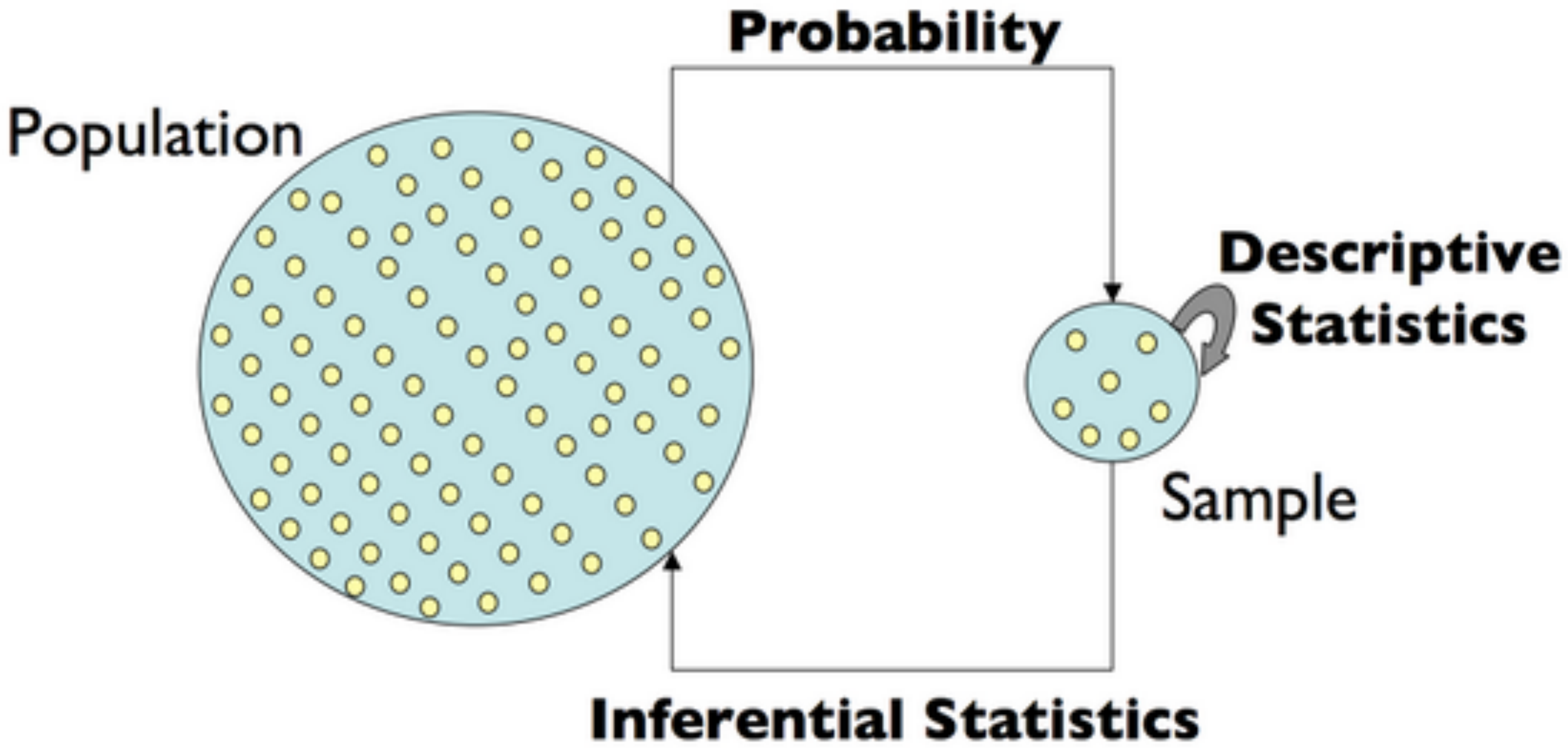
Learning objectives:

1. **Be familiar with the terminology**: describe data as random variables with various types of sampling distributions

2. **Gain intuition for the central concepts**: understand how statistical inference and modeling can help us learn about the properties of a population

Statistical Inference

A framework for generating conclusions about a population from a sample of noisy data



- Language of **probability** enables us to discuss *uncertainty* and make *predictions*
- **Statistical inference** enables us to make *conclusions* about the data
- We need both to learn from data

Variables

ⓘ Definition

Variable: an element, feature, or factor that is liable to vary or change

- In statistical terminology, a **variable** is an unknown quantity that we’d like to study
- Most research questions can be formulated as: “**What’s the relationship between two or more variables?**”

Random variables

ⓘ Definition

Random Variable (RV): A variable whose value results from the measurement of a quantity that is subject to variation (e.g. the *outcome* an experiment)

- Examples: a coin flip, a dice throw, the expression level of gene X
- An RV has a *probability distribution*

Distributions of Random Variables (RVs)

ⓘ Definition

Probability: A number assigned to an outcome/event that describes the extent to which it is likely to occur

- Probability must satisfy certain rules (e.g. be between 0 and 1)
- Probability represents the (long-term) *frequency* of an event

ⓘ Definition

Probability distribution: A mathematical function that maps outcomes/events to probabilities

Example experiment: Two coin tosses

- **Experiment:** Toss two coins
- **Sample space:** set of all possible outcomes $S = \{TT, HT, TH, HH\}$
- **Random Variable of interest:** number of heads

	Outcome	Number of Heads
TT		0
HT		1
TH		1
HH		2

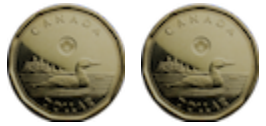
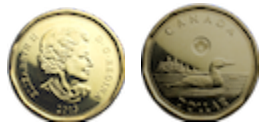
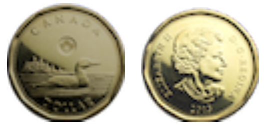
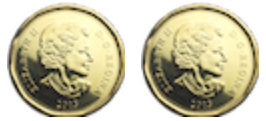
Assigning probability to outcomes

- Let:
  - $\omega =$ an outcome
  - $X(\omega) =$ number of heads in ω (RV)
- Each possible outcome is associated with a probability
- **Event:** A set of outcomes that satisfy some condition
- Each realization of the RV corresponds to an **event** (e.g. $X(\omega) = 1$ corresponds to the outcomes TH and HT)

	ω	$X(\omega)$	**Probability**
TT		0	0.25
HT		1	0.25
TH		1	0.25
HH		2	0.25

Assigning probability to events

The probability distribution of the Random Variable X tells us how likely each event (number of heads) is to occur in the experiment

Event	x	$P(X = x)$
	0	0.25
 , 	1	0.50
	2	0.25

Note on notation: $P(X = x)$ can also be written as $P_X(x)$

Two types of random variables

- A **discrete** RV has a countable number of possible values
  - e.g. throwing dice, genotype at a particular locus
- A **continuous** RV takes on values in an interval of numbers
  - e.g. blood glucose level, height of individuals

Discrete or Continuous?

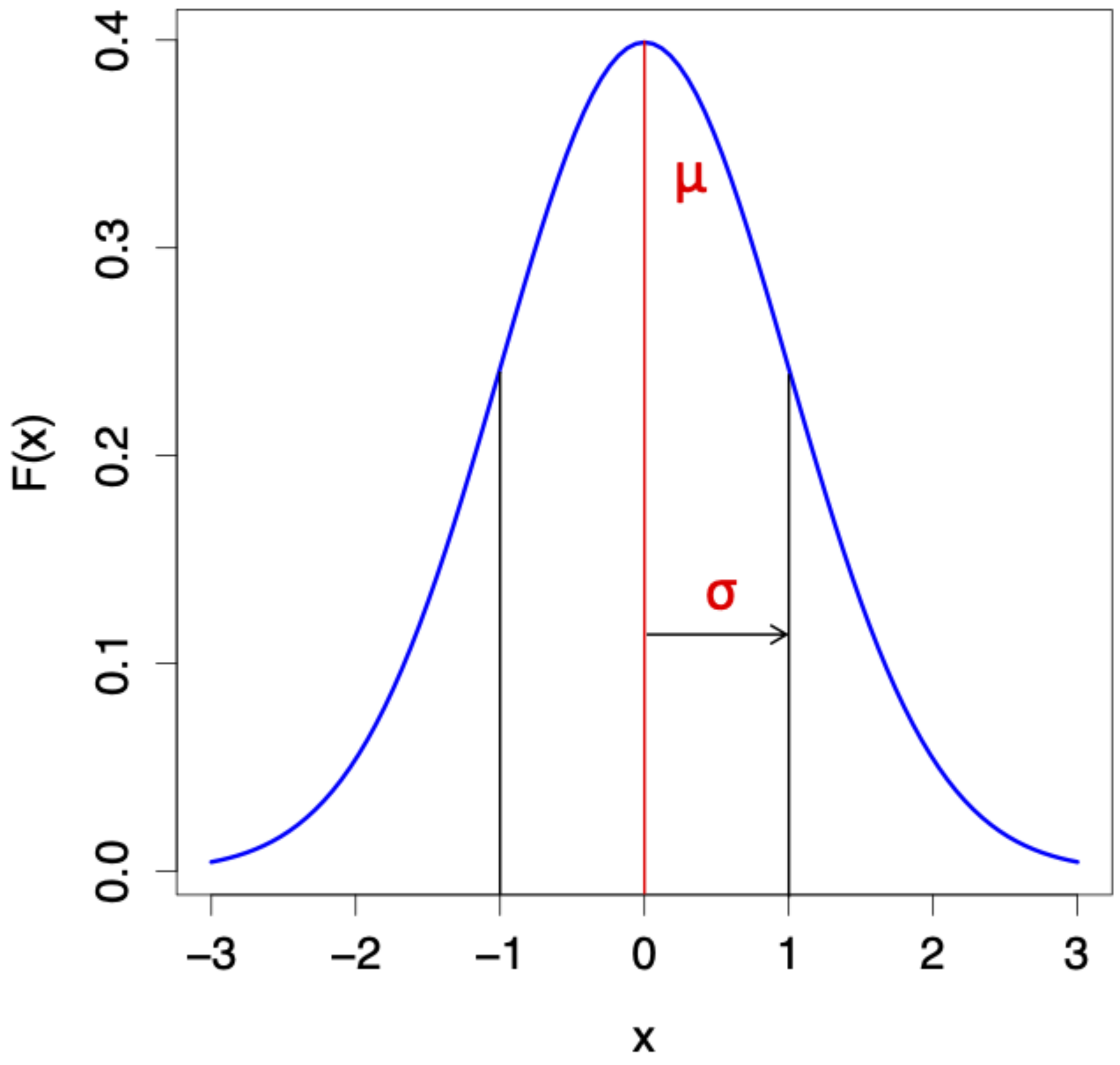
- survival time
- number of chromosomes
- mRNA expression level

Standard Gaussian (Normal) distribution

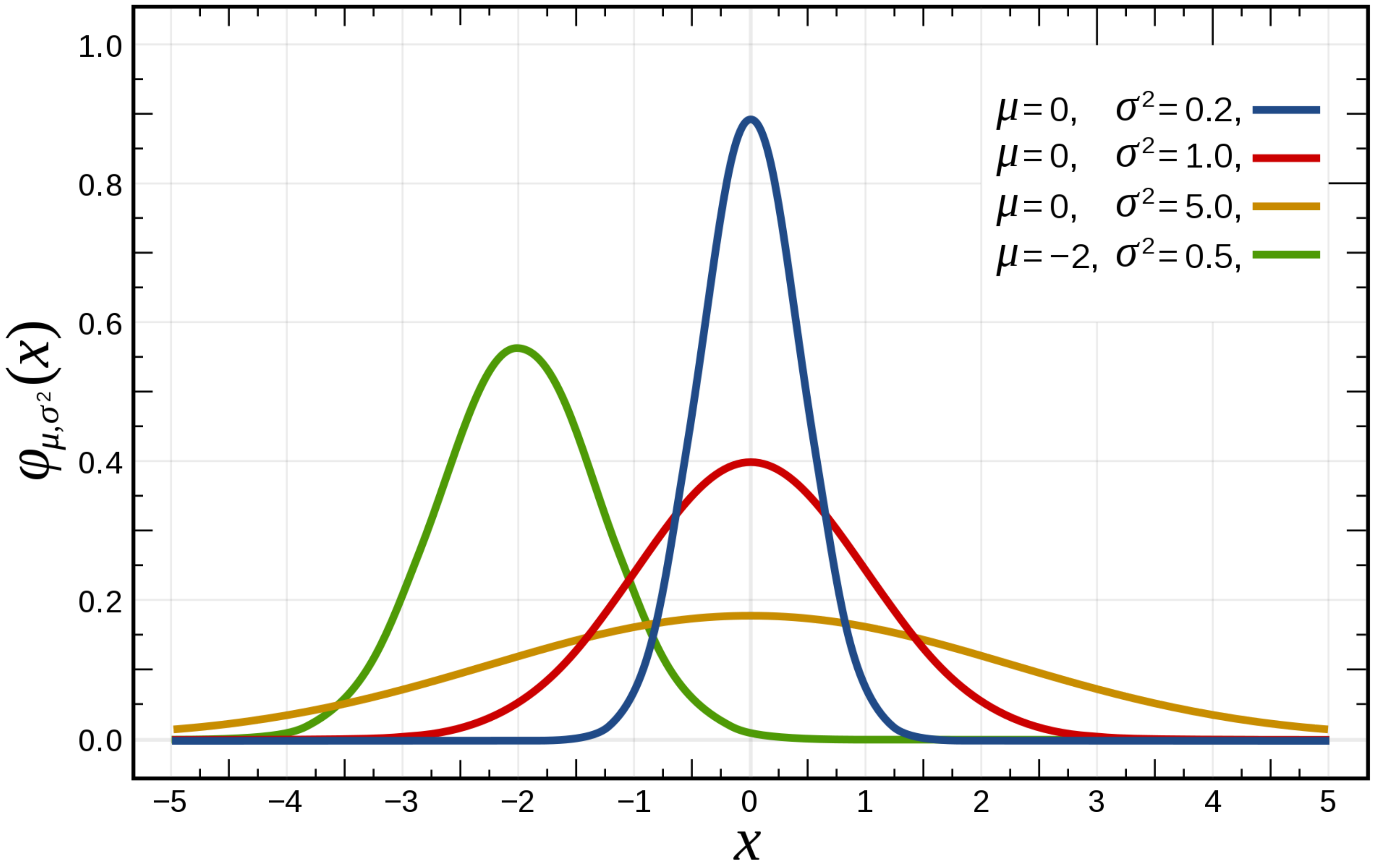
- probability density function (pdf):

$$f(x|\mu,\sigma^2) = \frac{1}{\sqrt{2\pi\sigma}} e^{-\frac{(x-\mu)^2}{2\sigma^2}}$$

- **Parameters**: quantities that summarize a population
  - Mean $= \mu$
  - Standard Deviation $= \sigma$
- For convenience, we write $N(\mu, \sigma^2)$
- When $\mu = 0$ and $\sigma = 1$, this is the *Standard* Normal distribution $N(0, 1)$

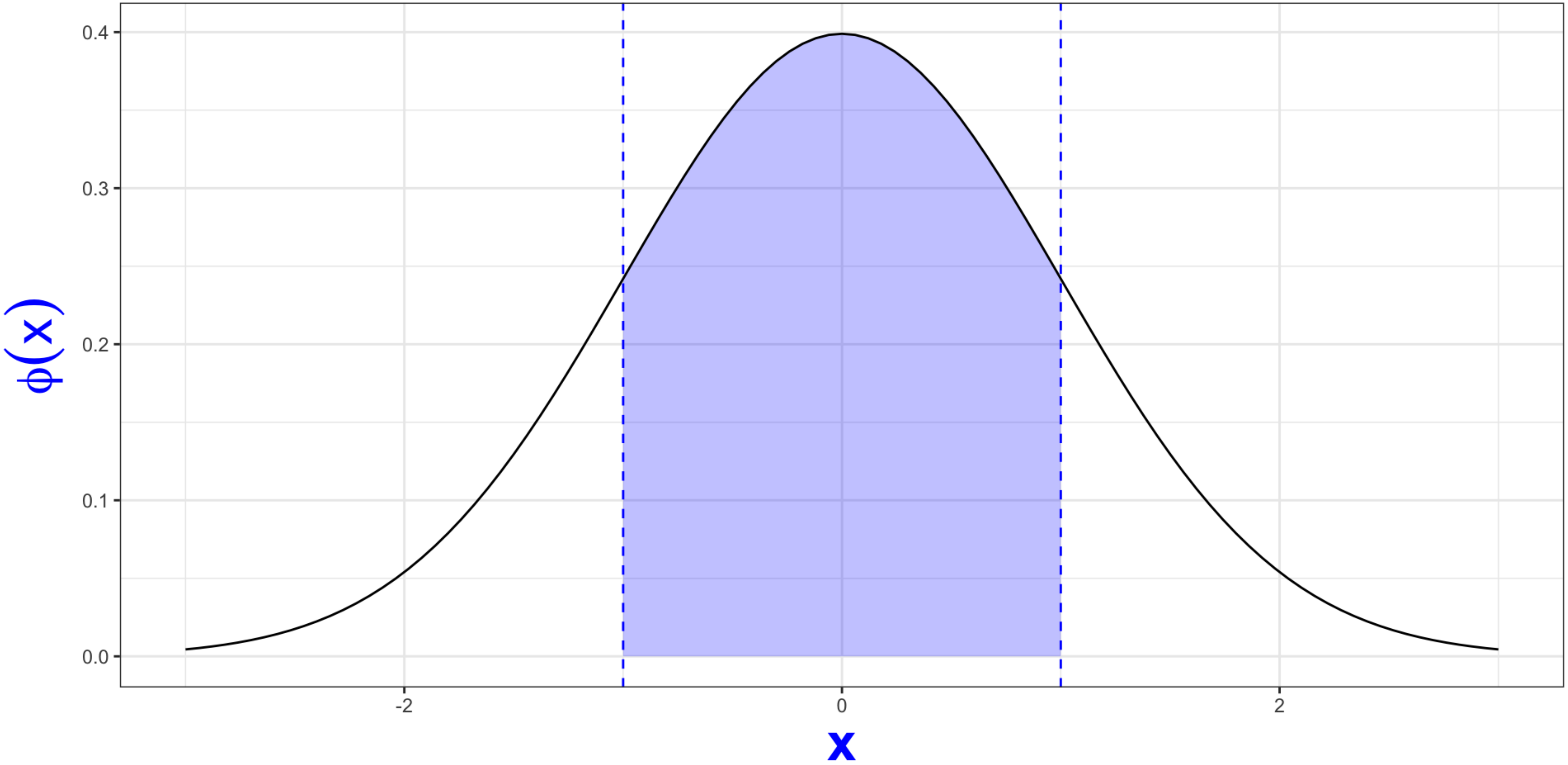


Gaussian (Normal) distribution

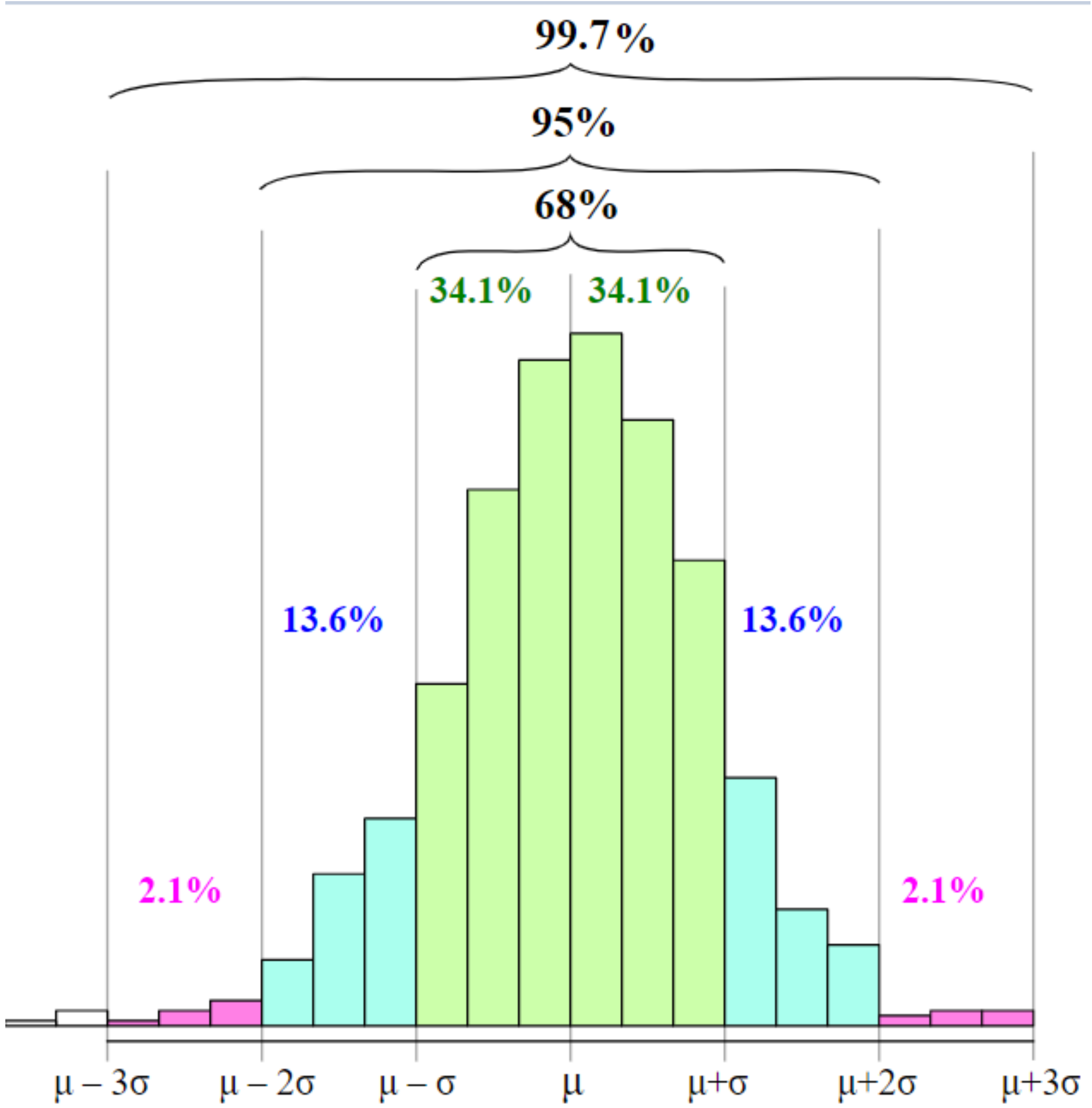


$$\text{pdf: } f(x|\mu,\sigma^2) = \phi(x) = \frac{1}{\sqrt{2\pi}\sigma} e^{-\frac{(x-\mu)^2}{2\sigma^2}}$$

Density → probability requires integration



Empirical Rule for Normal Distributions



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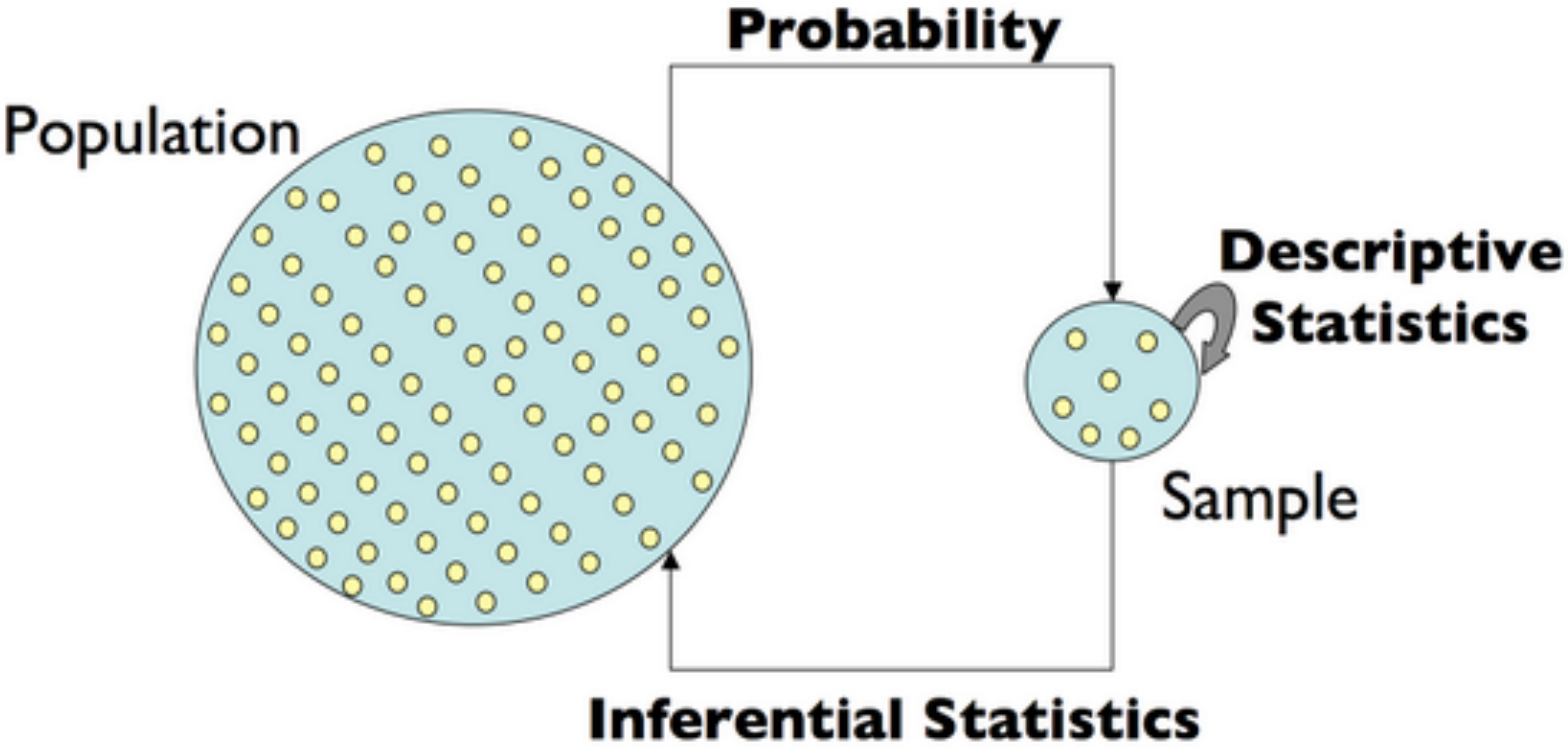
Statistical Inference

- The **parameter space** is the set of all possible values of a parameter
- One major goal: to “figure out” (i.e. estimate) the **parameter values**
  - i.e. *“fit the model to the data”*

> **Note**
>
> A **model** is a representation that (we hope) approximates the data and (more importantly) the population that the data were sampled from

- We can then use this model for:
  - hypothesis testing
  - prediction
  - simulation

Statistical Inference



IID

- A requirement (assumption) in many settings is that the data are **IID:** **I**ndependent and **I**dentically **D**istributed

- **Identically Distributed**: a set of observations (events) are from the same population
    - i.e. they have the same underlying probability distribution
    - e.g. a t-test assumes that under the null, all observations come from the same normal distribution
- **Independent**: Events A and B are independent if and only if $P(A, B) = P(A)P(B)$
    - i.e. the joint probability is the product of the individual event probabilities
    - The above statement is for two events, but the same definition applies for any number of events

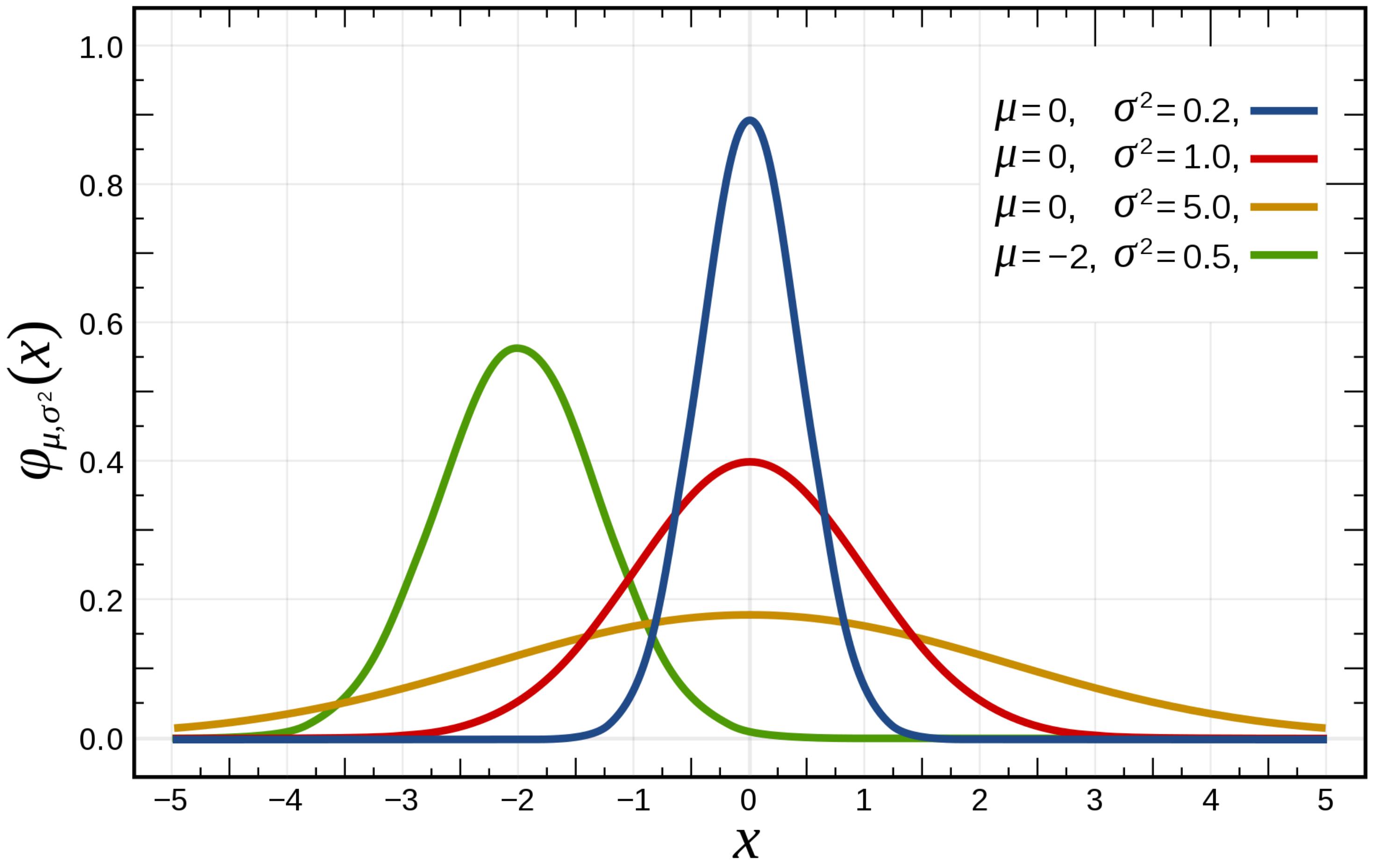
Violations of independence

Caution

If our analysis relies on the assumption that our observations are independent and they are not, our conclusions might be misleading

- Experimental design is in part about trying to avoid unwanted dependence
- Example of a design with unwanted dependence:
    - Height measurements of individuals sampled from *related* females in a particular family are **not** independent

Recall: parameters of the normal distribution



$$f(x|\mu,\sigma^2) = \frac{1}{\sqrt{2\pi}\sigma} e^{-\frac{(x-\mu)^2}{2\sigma^2}}$$

- Mean $= \mu$
- Standard Deviation $= \sigma$
- For convenience, we write $N(\mu, \sigma^2)$
- Population parameters are unknown

Parameter estimation

- **Estimator**: A function (or rule) used to estimate a parameter of interest
- **Estimate**: A particular realization (value) of an estimator

Estimators for normally distributed data

- If we are given a sample of n observations from a normally distributed population, how do we estimate the parameter values μ and σ?
- Recall μ is the mean and σ the standard deviation of the distribution

$$\hat{\mu} = \bar{x} = \frac{x_1 + x_2 + \ldots + x_n}{n} = \frac{1}{n} \sum_{i=1}^{n} x_i$$

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

Estimators vs Parameters

	Estimators	**Parameters**
Summarize	Sample	Population (ground truth)
Value	Computed from data	Unknown[1]
Notation	$\hat{\theta}$	θ

[1] almost always

Normal Mean: Estimator vs Parameter

	Estimator	**Parameter**
Summarizes	Sample/data	Population (ground truth)
Value	$\bar{x} = \frac{1}{n} \sum_{i=1}^{n} x_i$	Unknown[1]
Notation	$\hat{\mu}$	μ

[1] almost always

Normal Standard Deviation: Estimator vs Parameter

	Estimator	**Parameter**
Summarizes	Sample/data	Population (ground truth)
Value	$s = \sqrt{\frac{\sum_{i=1}^{n}(x_i-\bar{x})^2}{n-1}}$	Unknown[1]
Notation	$\hat{\sigma}$	σ

[1] almost always

Estimator for normally distributed data

- Let’s say we collected a **sample** from a population we assume to be normal
- We estimate the mean $\hat{\mu} = \bar{x}$
- How good is the estimate?

Sampling distribution

- **Statistic**: any quantity computed from values in a sample
- Any function (or statistic) of a sample (data) is a random variable
- Thus, any statistic (because it is random) has its own probability distribution function → specifically, we call this the **sampling distribution**
- Example: the sampling distribution of the mean

Sampling distribution of the mean

The sample mean $\bar{x}$ is a RV, so it has a probability or sampling distribution

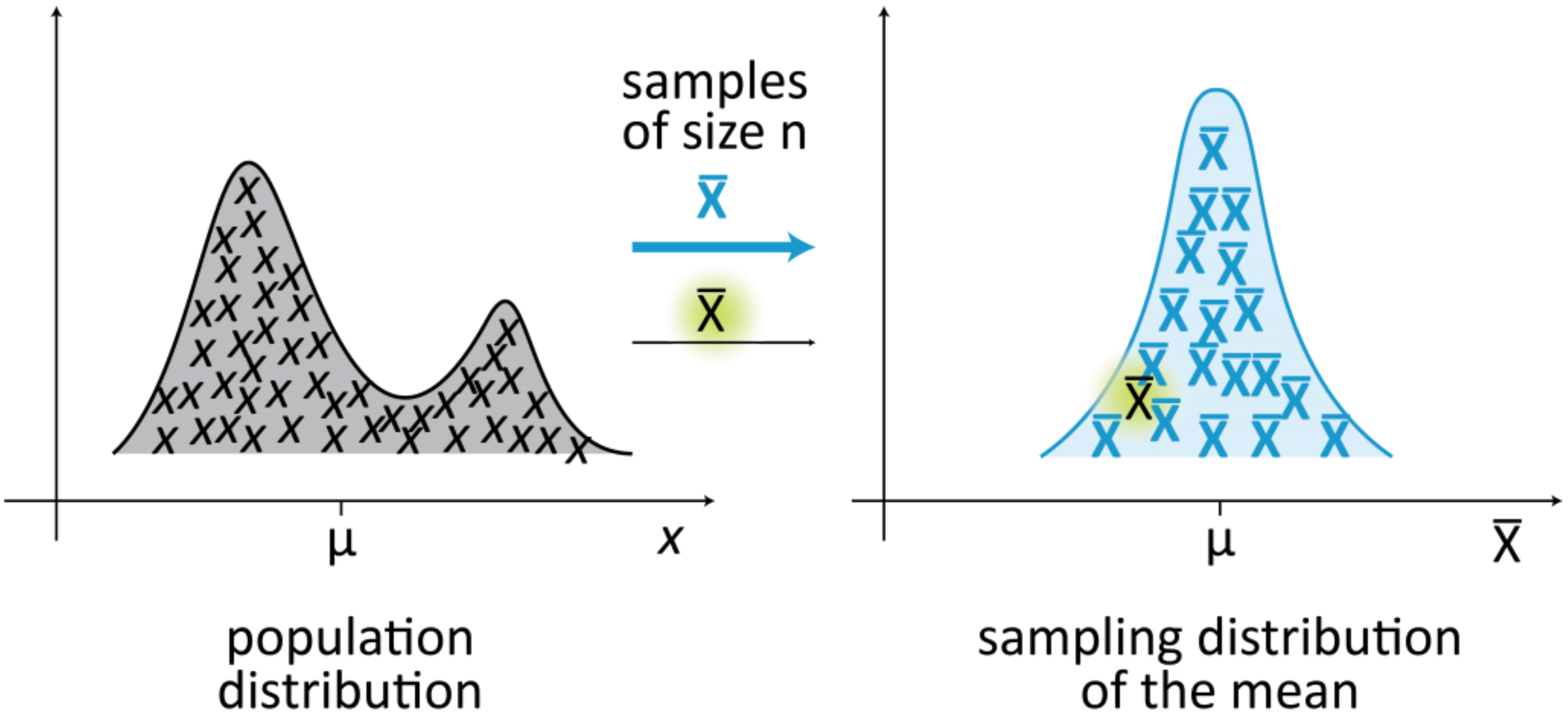


Image source: incertitudes.fr/book.pdf

Central Limit Theorem (CLT)

By the *Central Limit Theorem (CLT)*, we know that the sampling distribution of the mean (of n observations) is Normal with mean $\mu_{\bar{X}} = \mu$ and standard deviation $\sigma_{\bar{X}} = \frac{\sigma}{\sqrt{n}}$

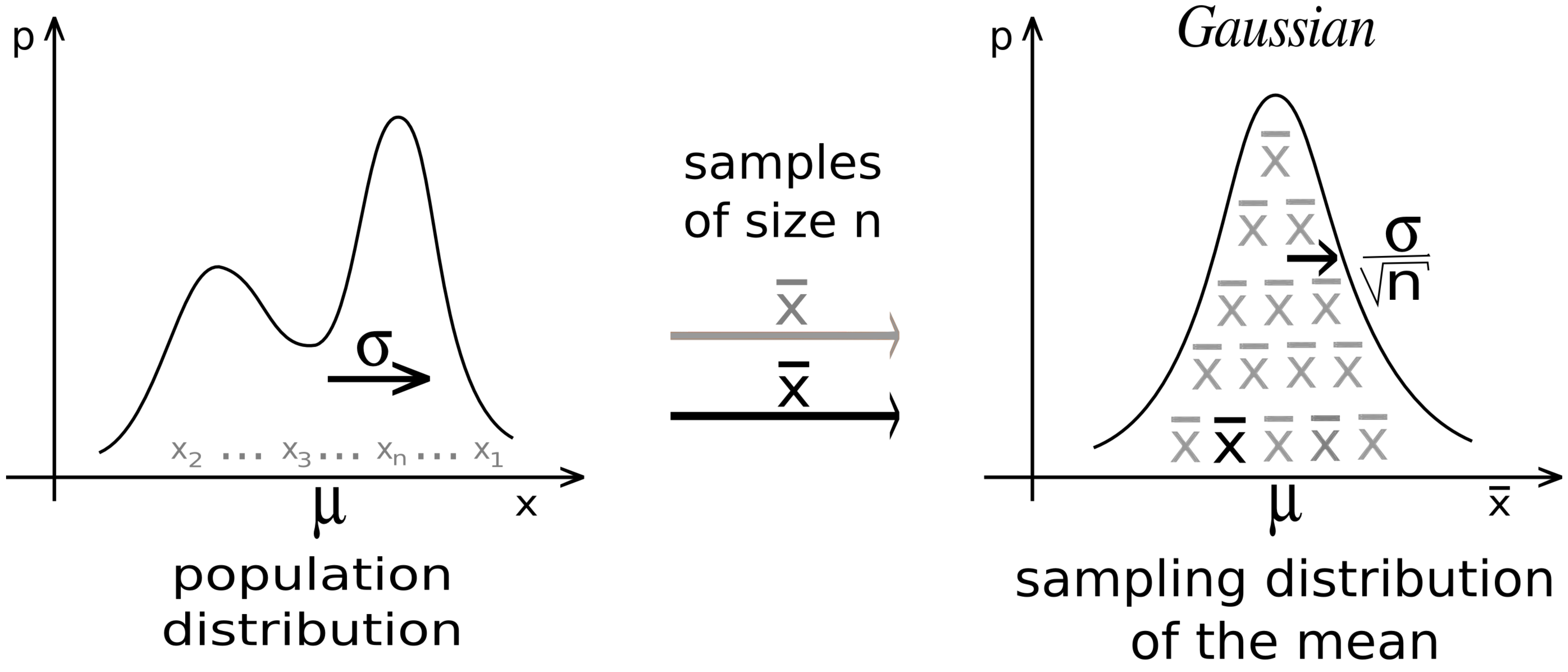

p
σ
x_2 ... x_3 ... x_n ... x_1
μ
x
population distribution
samples of size n
$\bar{x}$
$\bar{x}$
p
Gaussian
$\bar{x}$
$\frac{\sigma}{\sqrt{n}}$
μ
$\bar{x}$
sampling distribution of the mean

Image source: incertitudes.fr/book.pdf

Standard deviation vs standard error

⚠ **Warning**

The standard deviation is not the same as the standard error

- The sampling distribution of the mean of n observations (by CLT):

$$\bar{X} \sim N(\mu, \frac{\sigma^2}{n})$$

- The *standard error* of the mean is $\frac{\sigma}{\sqrt{n}}$
- The *standard deviation* of X is σ

Estimation of parameters of the sampling distribution of the mean

Just as we estimated μ and σ before, we can estimate $\mu_{\bar{X}}$ and $\sigma_{\bar{X}}$

- $\hat{\mu}_{\bar{X}} = \hat{\mu} = \bar{x}$
- $\hat{\sigma}_{\bar{X}} = \frac{\hat{\sigma}}{\sqrt{n}} = \frac{s}{\sqrt{n}}$

Standard error of the mean

$$\hat{\sigma}_{\bar{X}} = \frac{\hat{\sigma}}{\sqrt{n}} = \frac{s}{\sqrt{n}}$$

- The standard error (SE) of the mean reflects uncertainty about our estimate of the population mean $\hat{\mu}$
- For the distributional assumptions to hold, the CLT assumes a ‘large enough’ sample:
  - when the sample size is ~30 or more, the normal distribution is a good approximation for the sampling distribution of the mean
  - for smaller samples, the SE $\frac{s}{\sqrt{n}}$ is an underestimate

CLT applies to any population…

…regardless of distribution

Let $X_1, X_2, \ldots, X_n$ be a random sample from a population with a non-normal distribution. If the sample size n is sufficiently large, then the sampling distribution of the mean will be approximately normal:

$$\bar{X} \sim N(\mu, \frac{\sigma^2}{n})$$

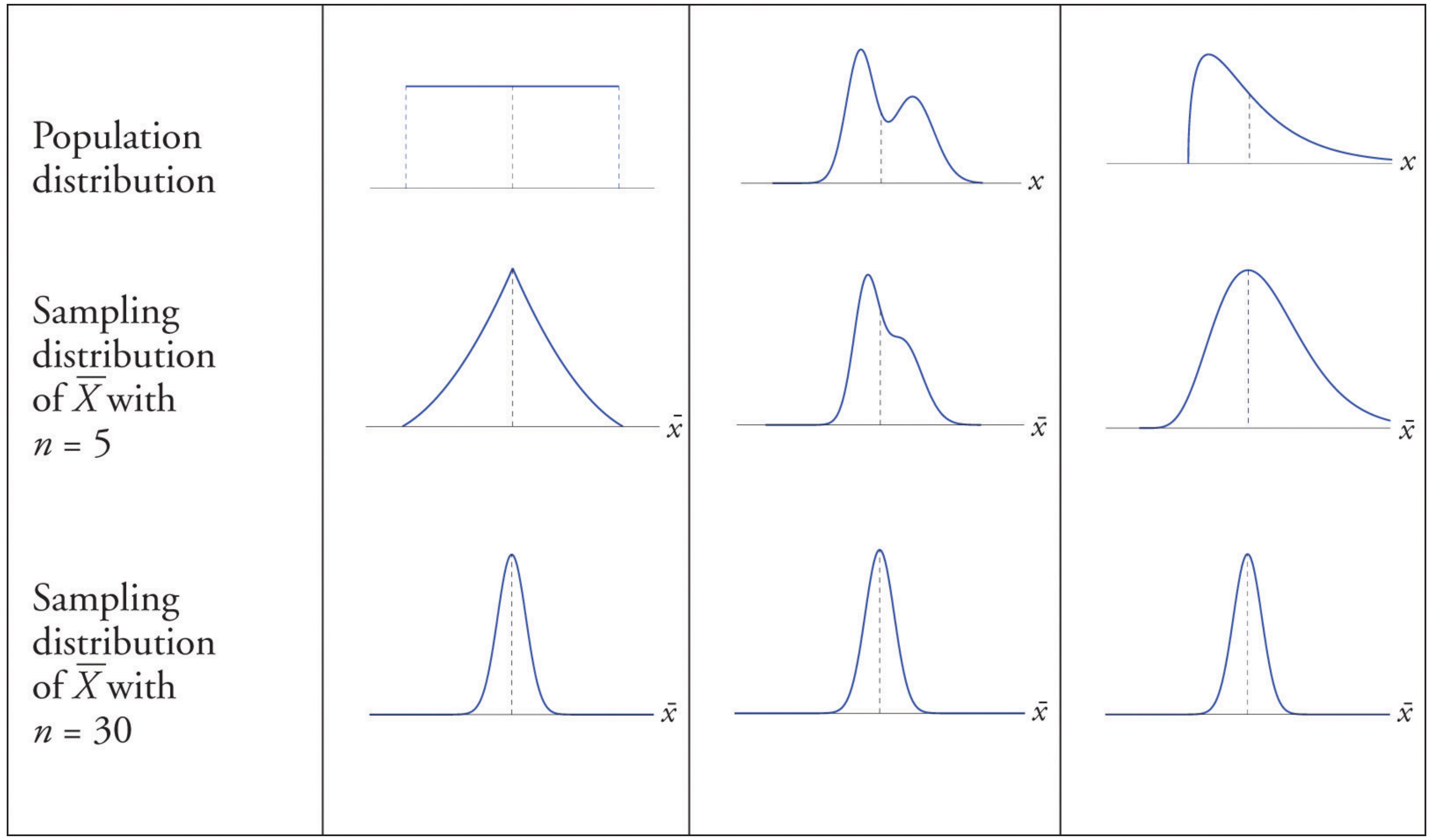
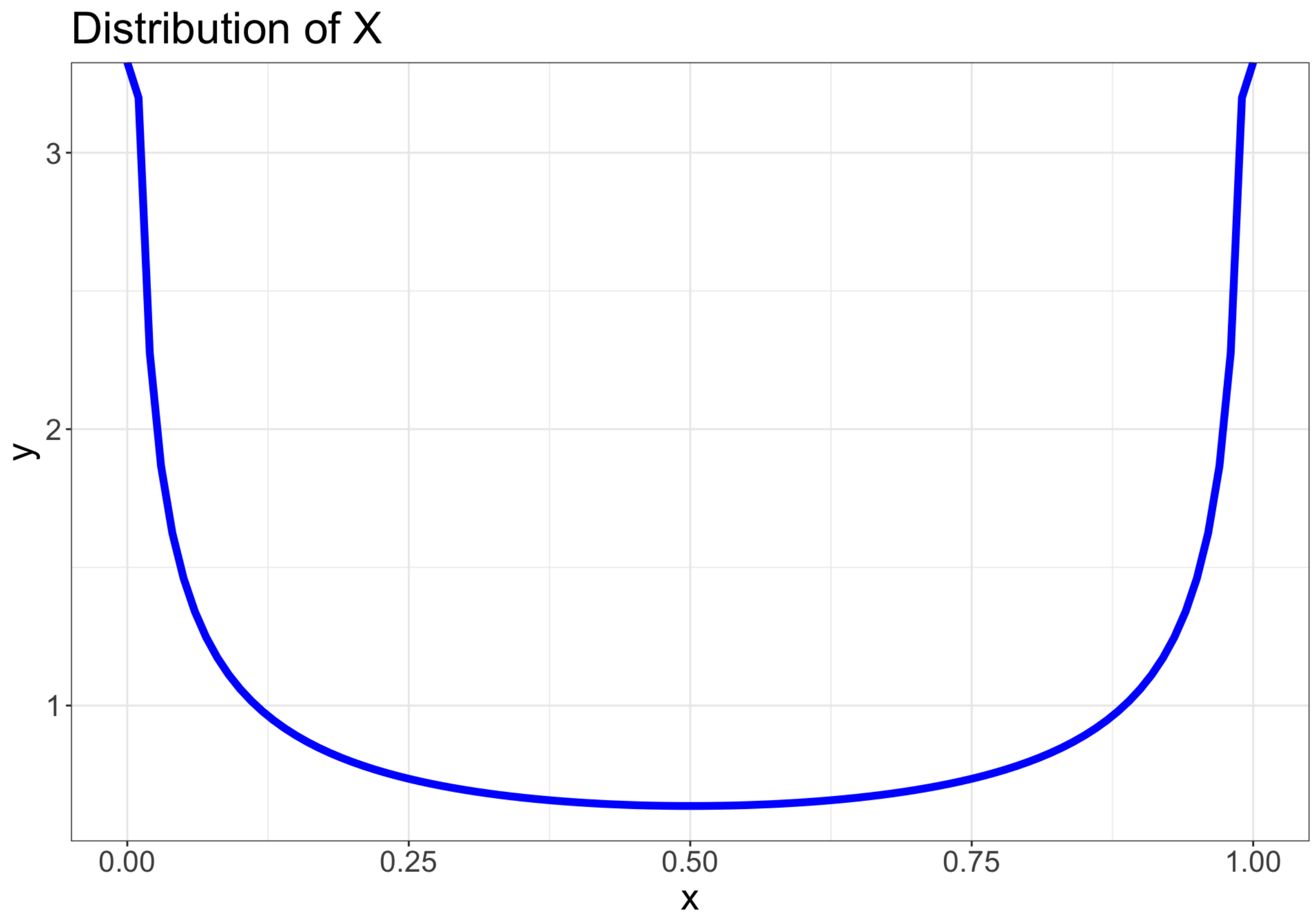
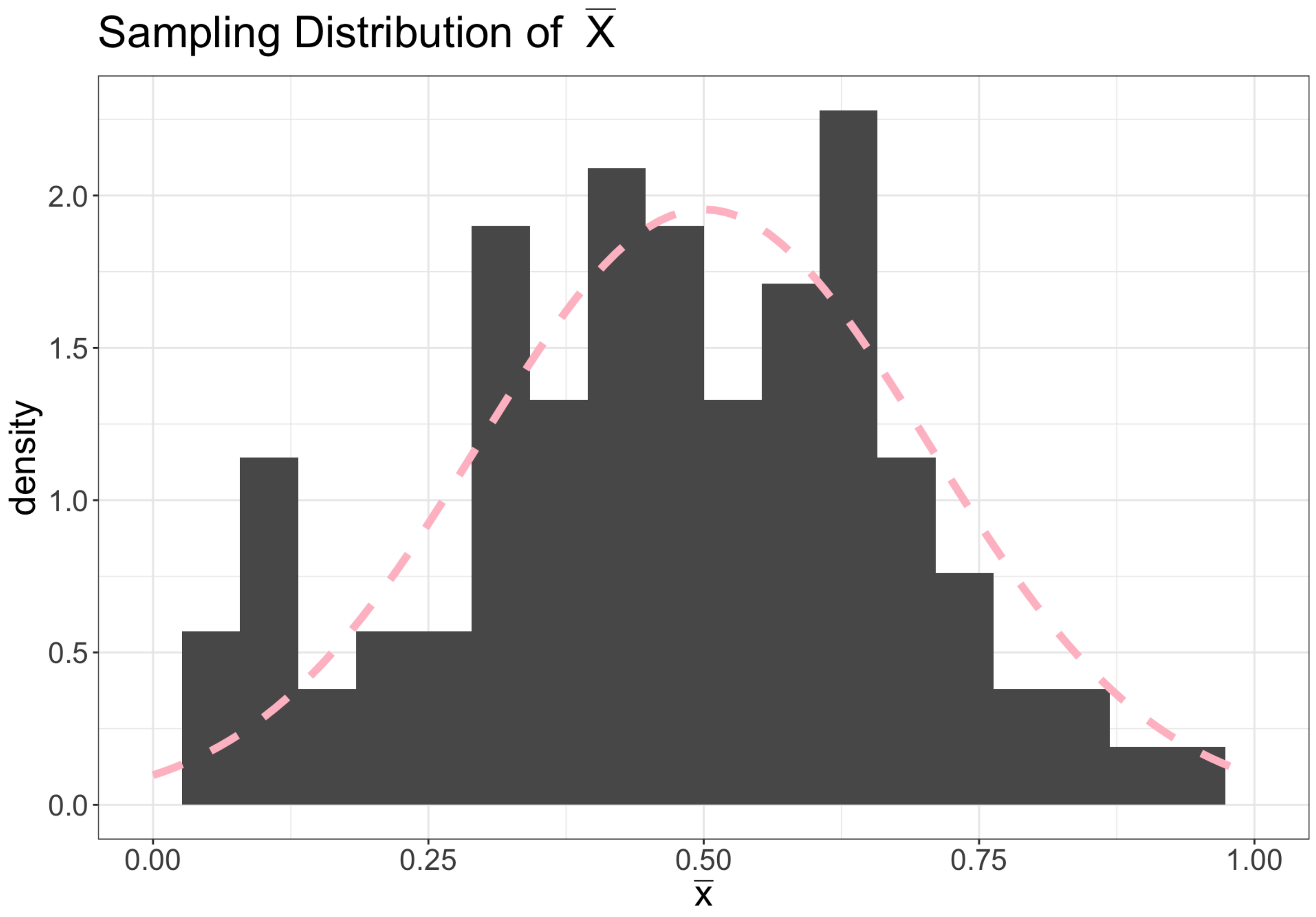


Image source: saylordotorg.github.io/text_introductory-statistics

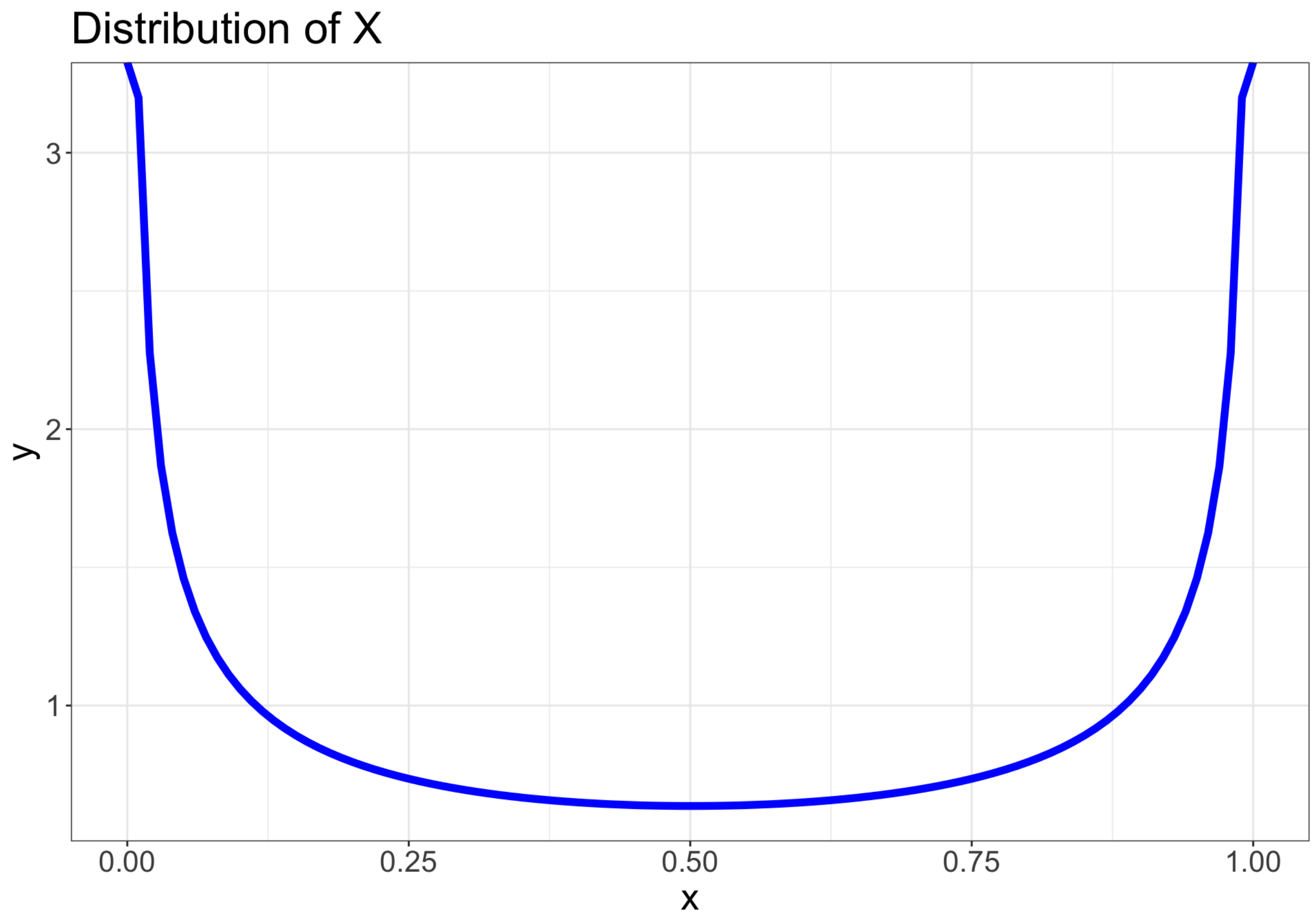
Illustration (n = 3)



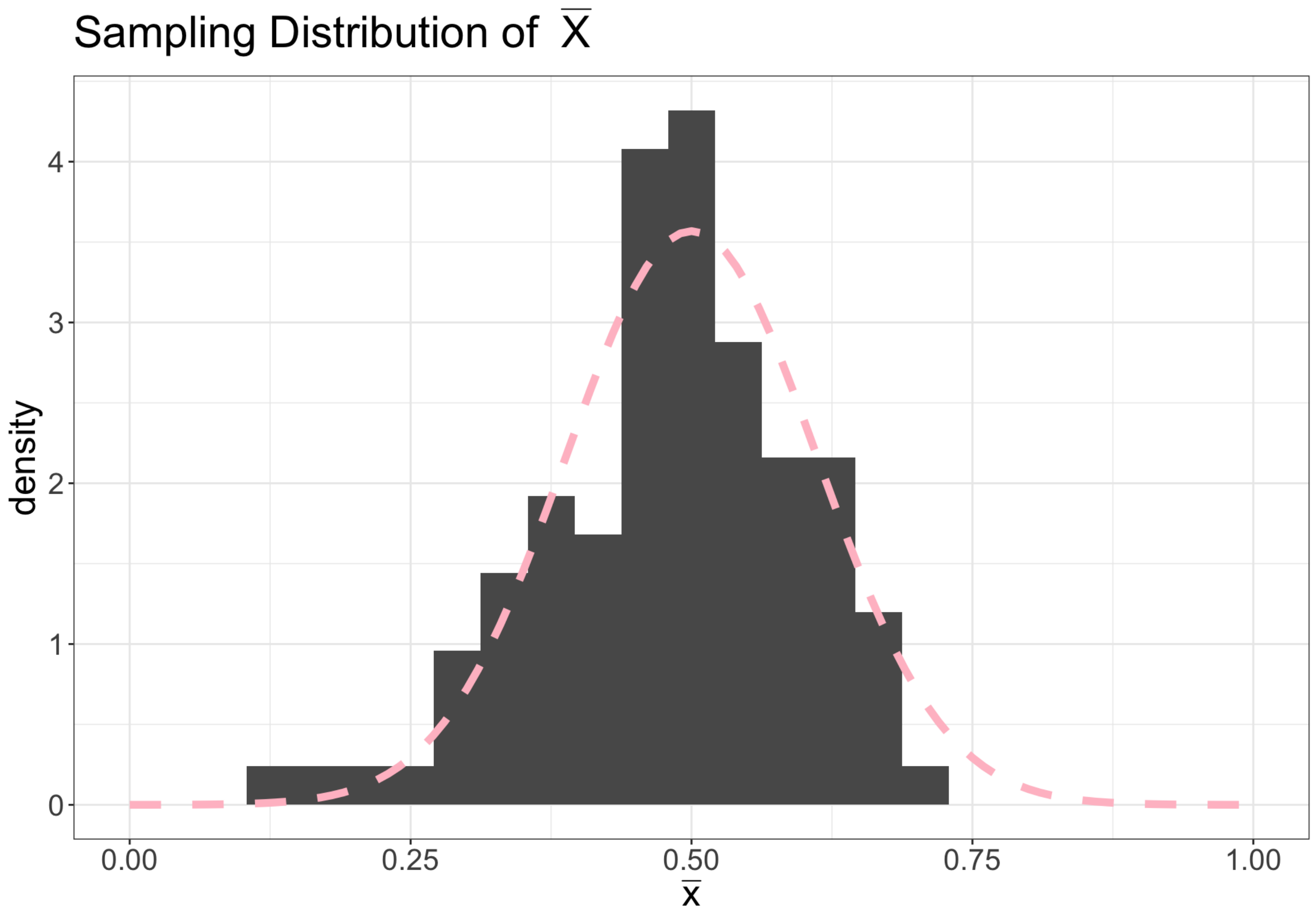


On right: dashed pink line is $N(\mu, \sigma^2/n)$

Illustration (n = 10)



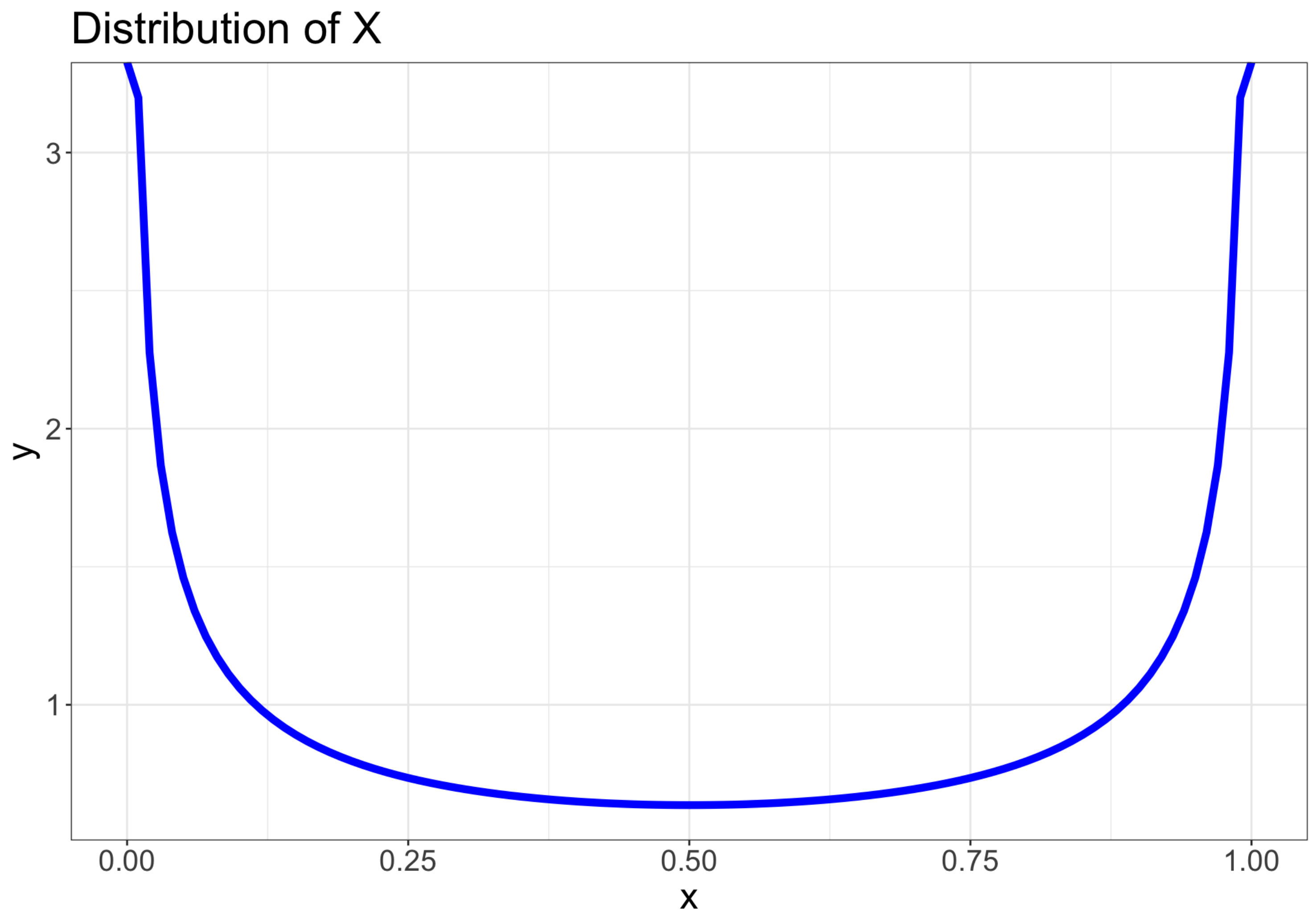
Distribution of X

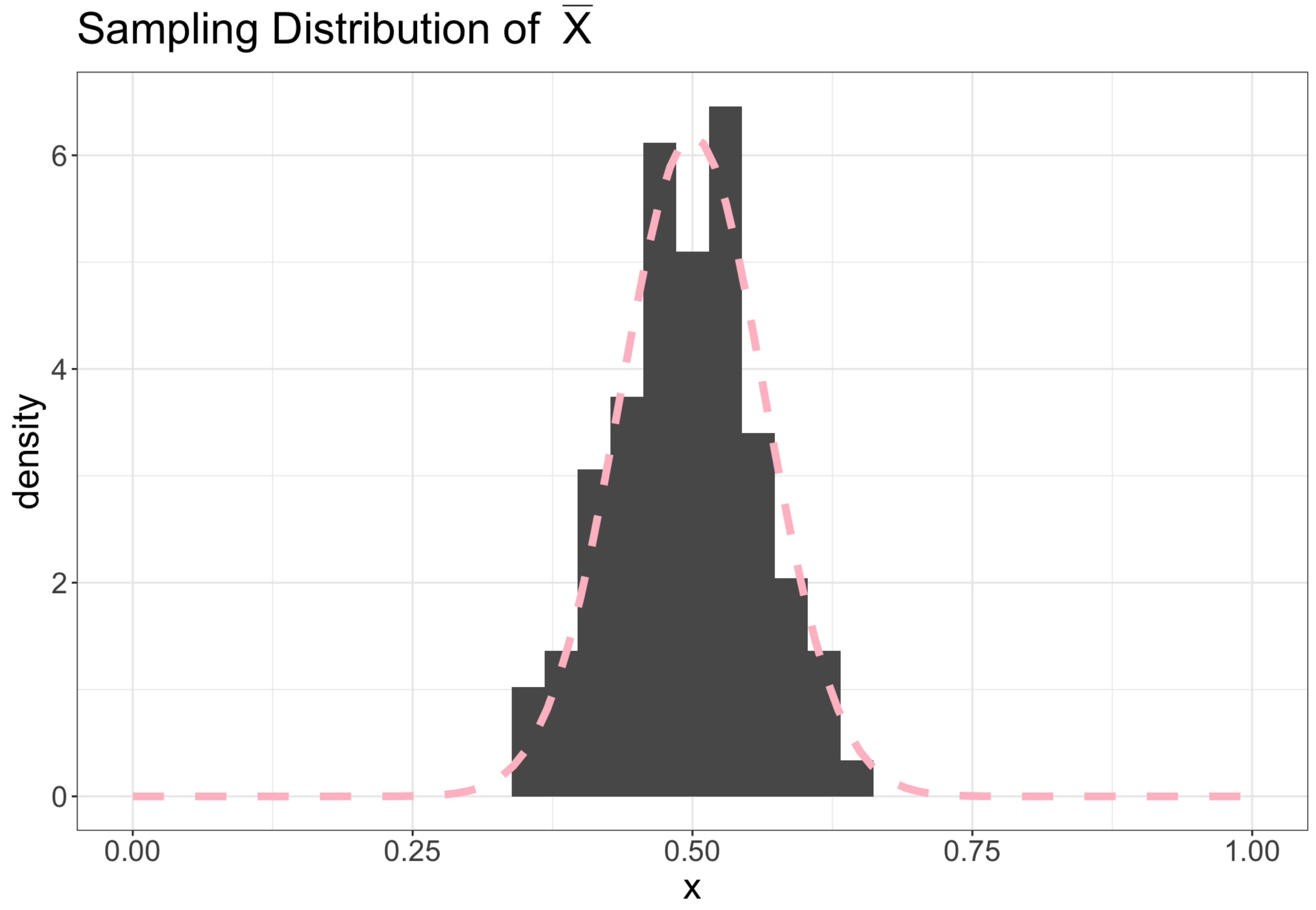


Sampling Distribution of $\overline{X}$

On right: dashed pink line is $N(\mu, \sigma^2/n)$

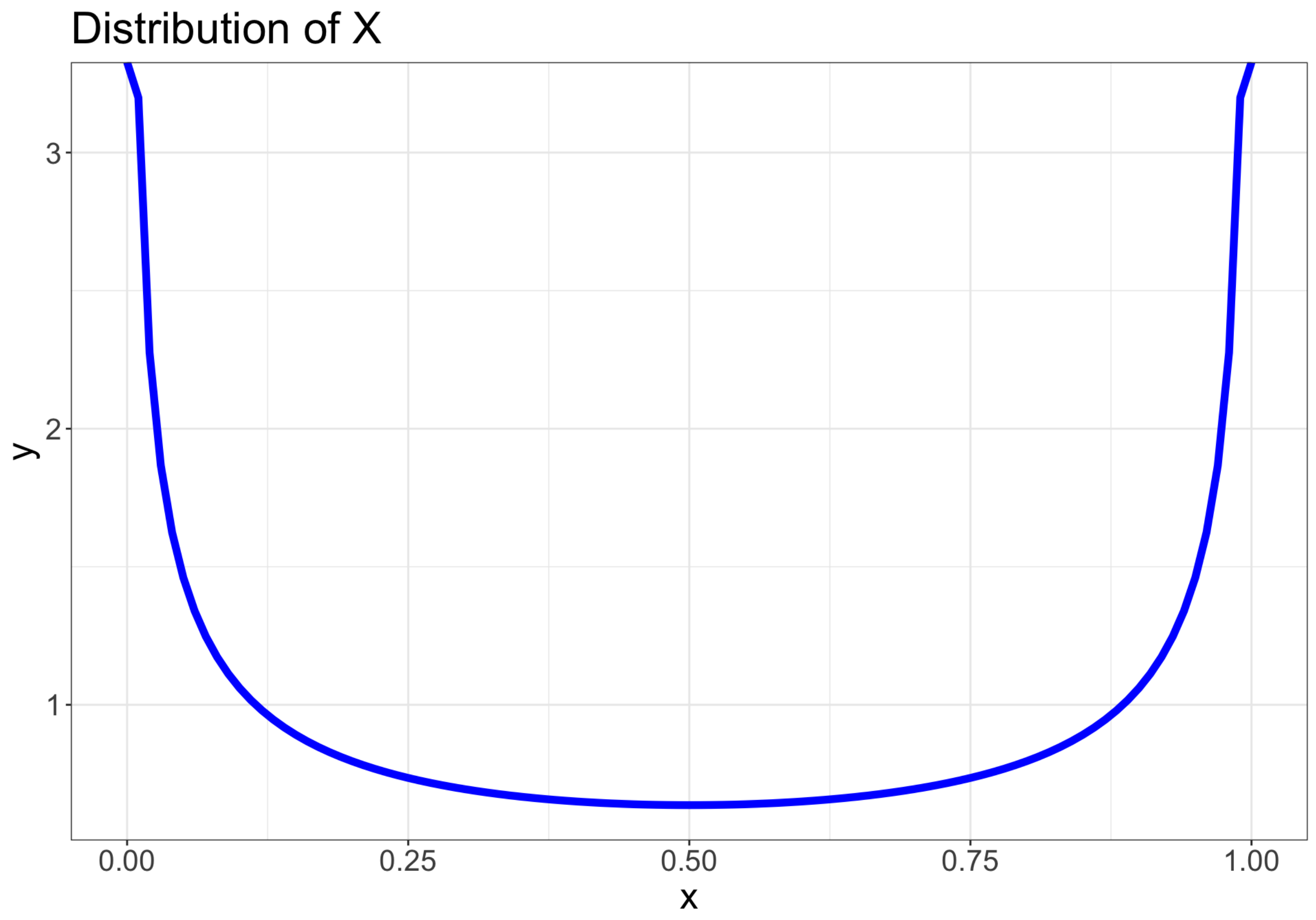
Illustration (n = 30)

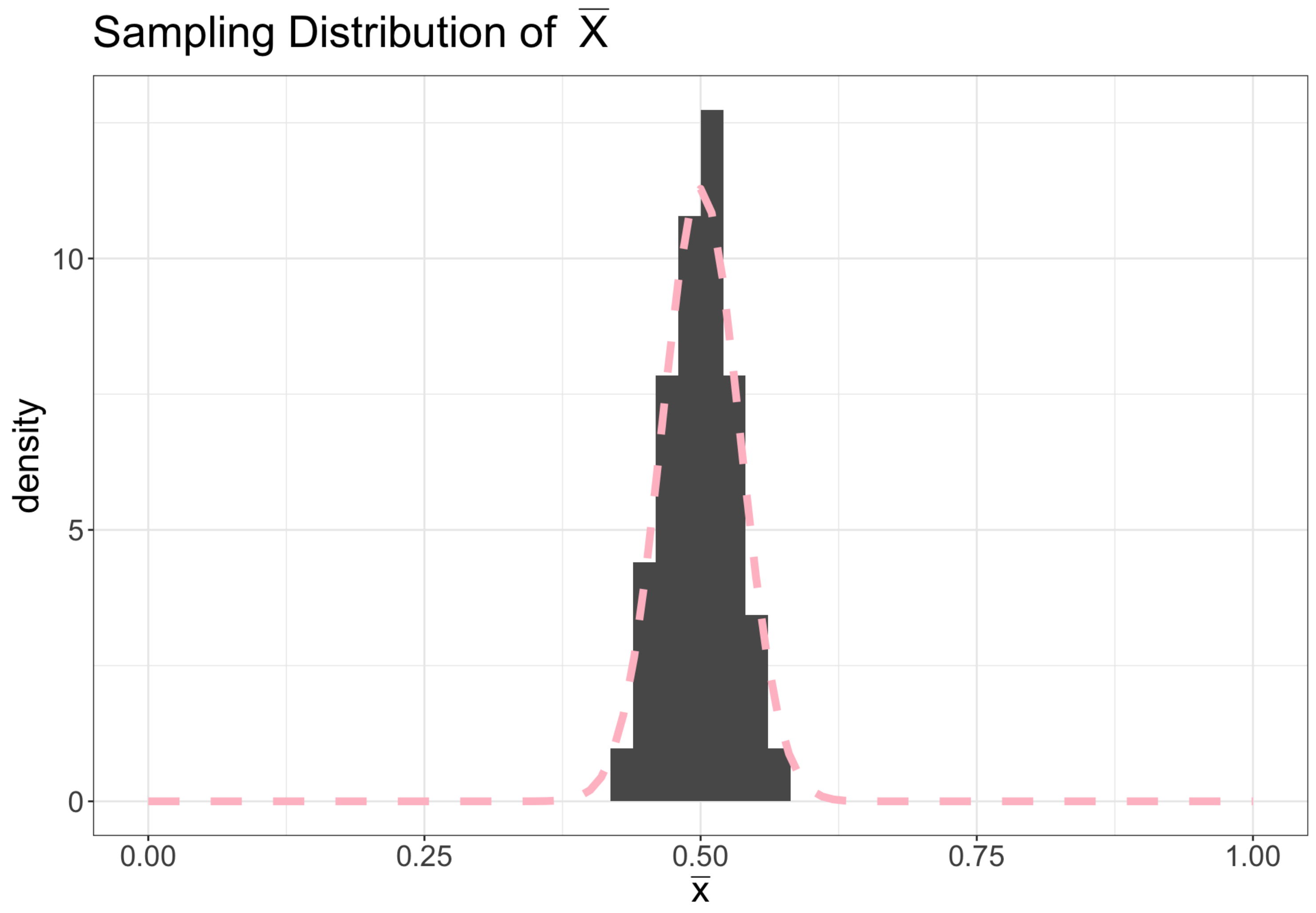




On right: dashed pink line is $N(\mu, \sigma^2/n)$

Illustration (n = 100)


Distribution of X


Sampling Distribution of $\overline{X}$

On right: dashed pink line is $N(\mu, \sigma^2/n)$

Hypothesis Testing

- **Hypothesis:** A *testable (falsifiable)* idea for explaining a phenomenon
- **Statistical hypothesis:** A hypothesis that is testable on the basis of observing a process that is modeled via a set of random variables
- **Hypothesis Testing:** A formal procedure for determining whether to *accept* or *reject* a statistical hypothesis
- Requires comparing two hypotheses:
  - H_0: null hypothesis
  - H_A or H_1: alternative hypothesis

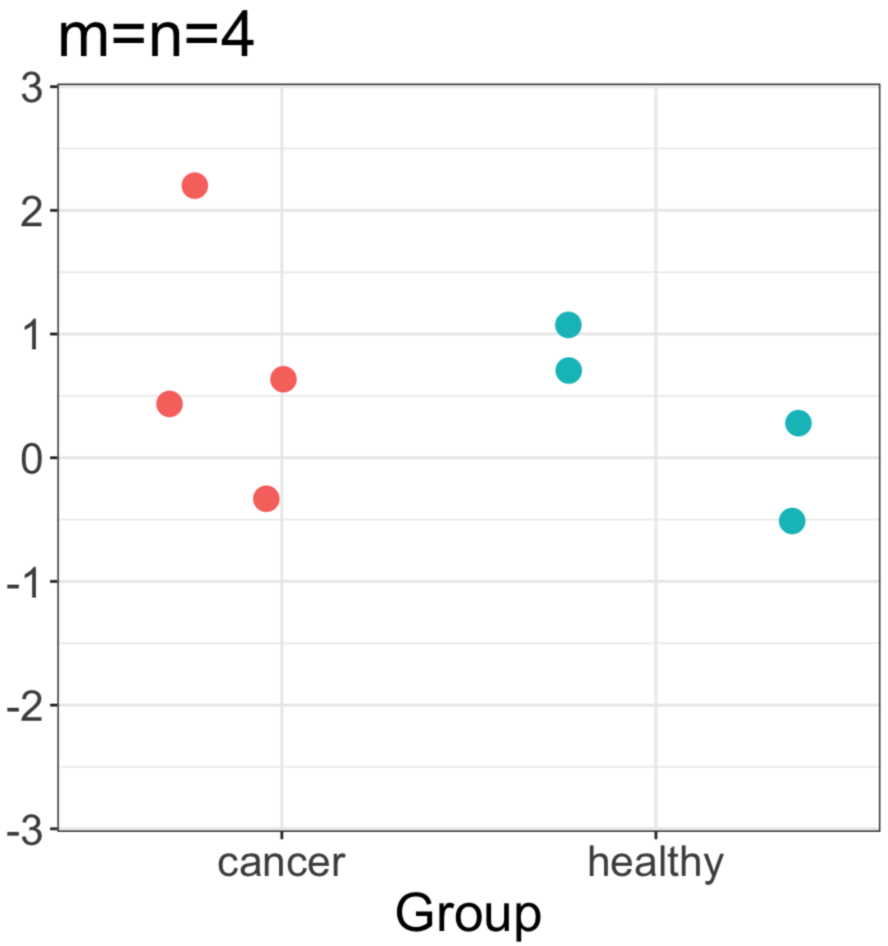
Hypothesis Testing: Motivating Example

- The expression level of gene g is measured in n patients with disease (e.g. cancer), and m healthy (control) individuals:
  - $z_1, z_2, \ldots, z_n$ and $y_1, y_2, \ldots, y_m$
- Is gene g differentially expressed in cancer vs healthy samples?
  - $H_0 : \mu_Z = \mu_Y$
  - $H_A : \mu_Z \neq \mu_Y$
- In this setting, hypothesis testing allows us to determine whether observed differences between groups in our data are *significant*

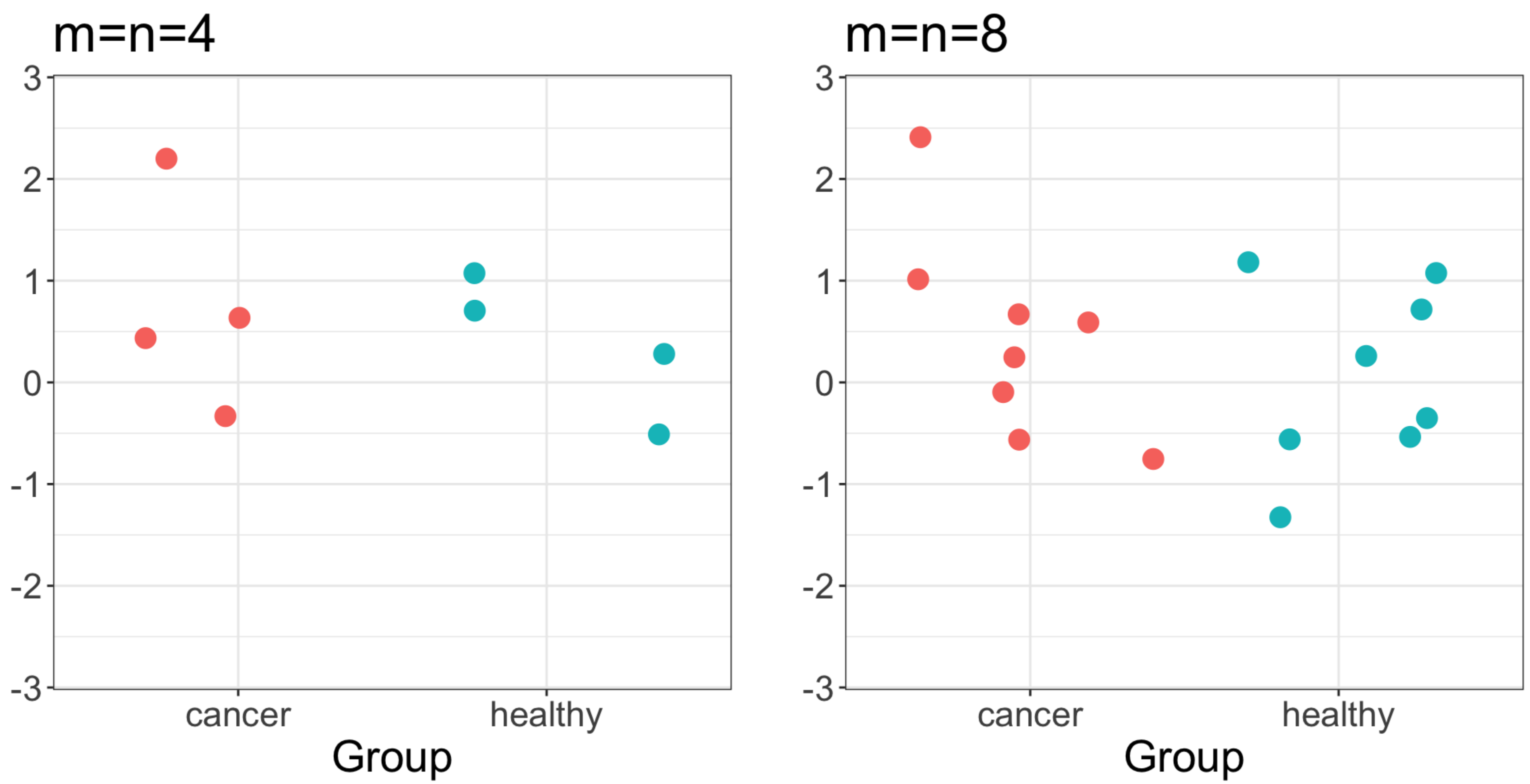
Steps in Hypothesis Testing

1. Formulate your hypothesis as a statistical hypothesis
2. Define a test statistic t (RV) that corresponds to the question. You typically know the expected distribution of the test statistic *under the null*
3. Compute the p-value associated with the observed test statistic under the null distribution $p(t|H_0)$

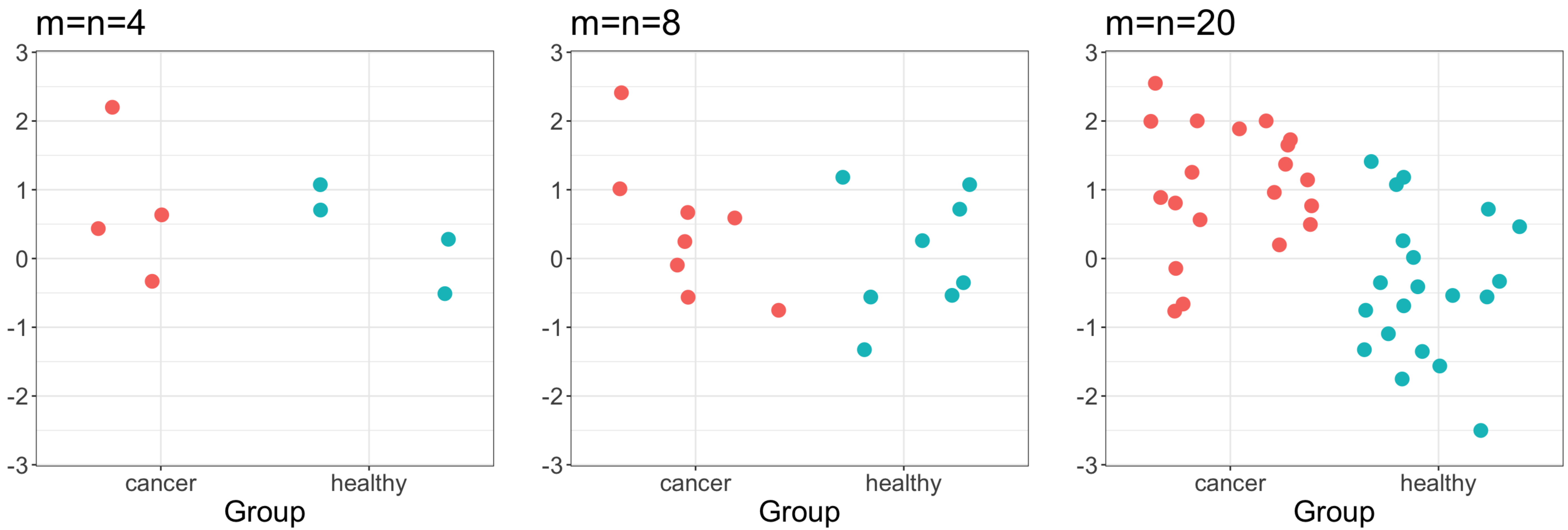
Motivating example (cancer vs healthy gene expression)



Motivating example (cancer vs healthy gene expression)

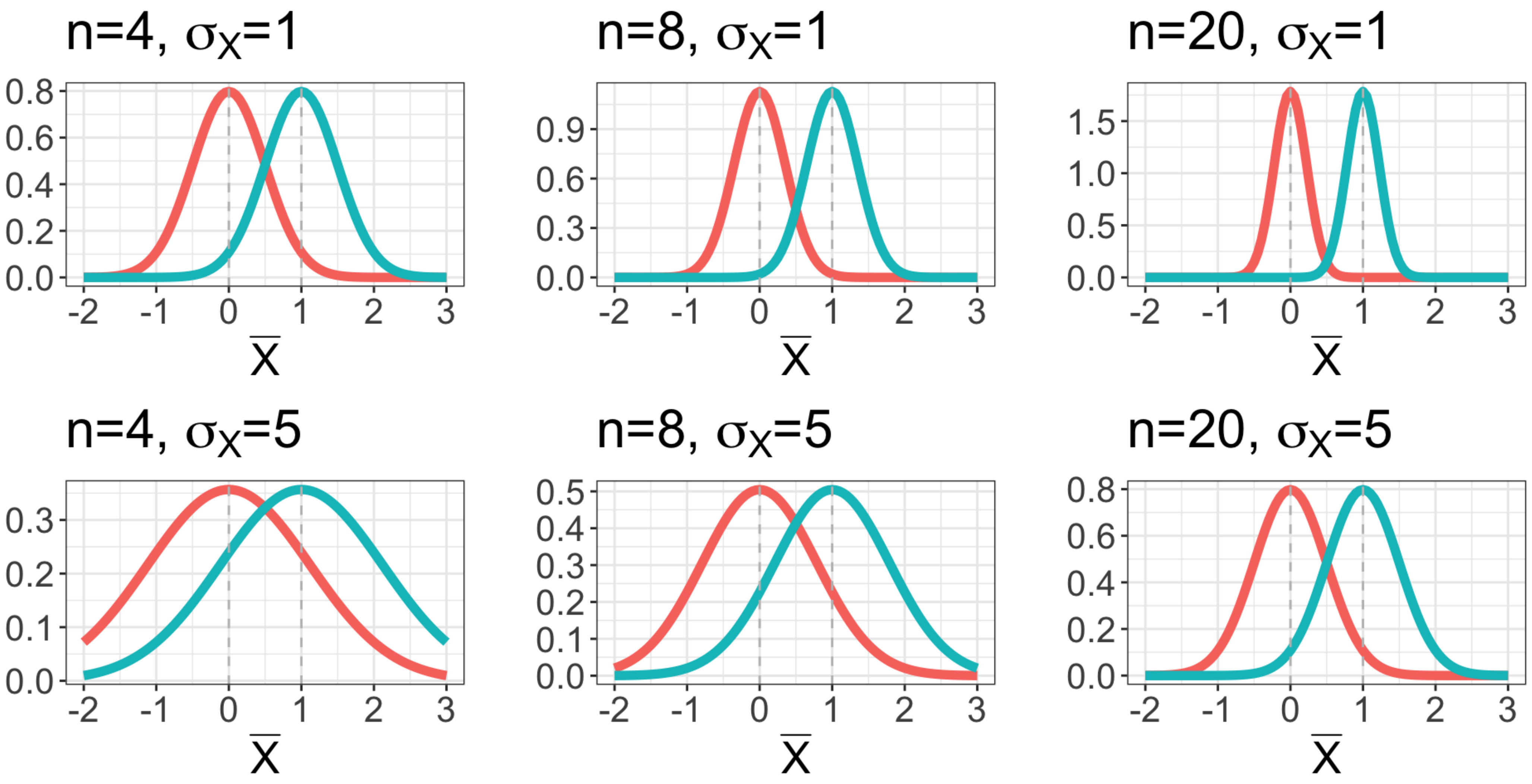


Motivating example (cancer vs healthy gene expression)



- Is there a **significant** difference between the two means?
- All three samples drawn from **iid** Normal distributions with equal variance and $\mu_Z - \mu_Y = 1$

Is there a significant difference between the two means?



Mean difference needs to be put into context of the *spread (standard deviation)* and *sample size*. This shouldn't be surprising when we recall the formula for the **sampling distribution of the mean:** $\bar{X} \sim N(\mu, \frac{\sigma^2}{n})$

2 sample t-statistic

- **2-sample t-statistic:** measures difference in means, adjusted for spread/standard deviation:

$$t = \frac{\bar{z} - \bar{y}}{SE_{\bar{z}-\bar{y}}}$$

e.g. for $z_1, z_2, \ldots, z_n$ expression measurements in healthy samples and $y_1, y_2, \ldots, y_m$ cancer samples

- From the theory, we know the distribution of our test statistic, if we are willing to make some assumptions

2 sample t-test

- If we assume:
  - $\bar{Z}$ and $\bar{Y}$ are normally distributed
  - Z and Y have equal variance
- Then the standard error estimate for the difference in means is:

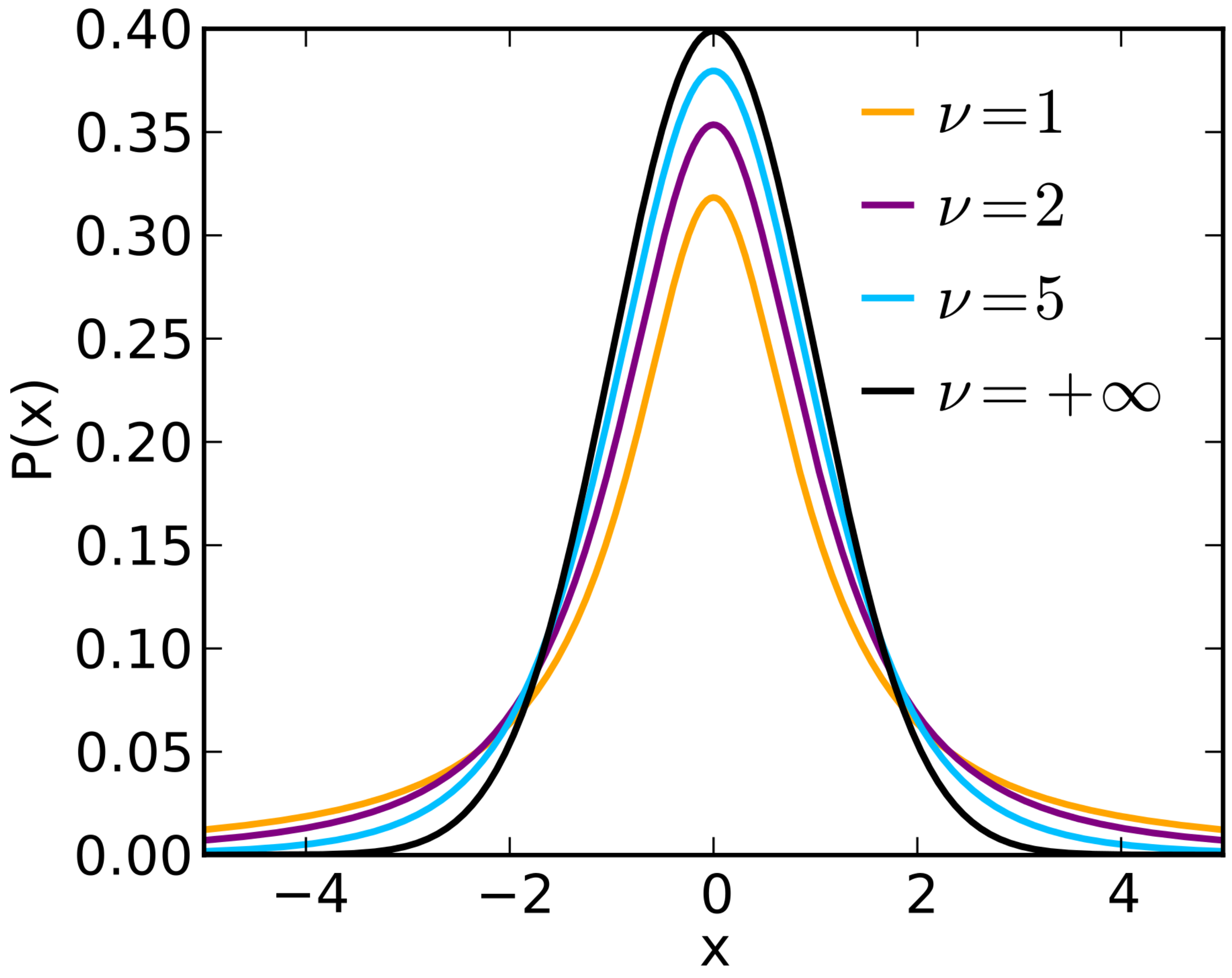
$$SE_{\bar{z}-\bar{y}} = s_p \sqrt{\frac{1}{n} + \frac{1}{m}}, \text{ where } s_p^2 = \frac{s_z^2 + s_y^2}{(n-1)+(m-1)}$$

- And our t-statistic follows a t distribution with m+n-2 degrees of freedom

$$t \sim t_{n+m-2}$$

- (Alternative formulations for unequal variance setting)

t distribution



- statistic value tells us how extreme our observed data is relative to the null
- obtain **p-value** by computing area to the left and/or right of the t statistic (one-sided vs two-sided)

Summary

- Random variables are variables that have a probability distribution
- Any statistic of sampled data is a RV, and hence has an associated probability distribution
- The CLT gives us the sampling distribution of the mean of any RV (regardless of its distribution)
- We can use statistical inference to estimate population parameters from a sample
- Hypothesis testing gives us a framework to assess a statistical hypothesis under the null