UCLA QCBio Collaboratory

Introduction to Modern Statistics

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2025 Winter

UCLA Bioinformatics

Notation of the slides

- `Code` or `Pseudo-Code` chunk starts with " ➢ ", e.g.
  - ➢ `print("Hello world!")`

- Link is underlined

- Important terminology is in **bold** font

- Practice comes with

Agenda

- Day 1: Probability and Statistics basics
  - Uncertainty; Probability; Distribution
  - Descriptive statistics
- Day 2: Inference
  - Hypothesis testing and *p*-values
  - Permutation test and bootstrap
  - False discovery rate control
- Day 3: Modeling
  - Regression techniques
  - Model selection

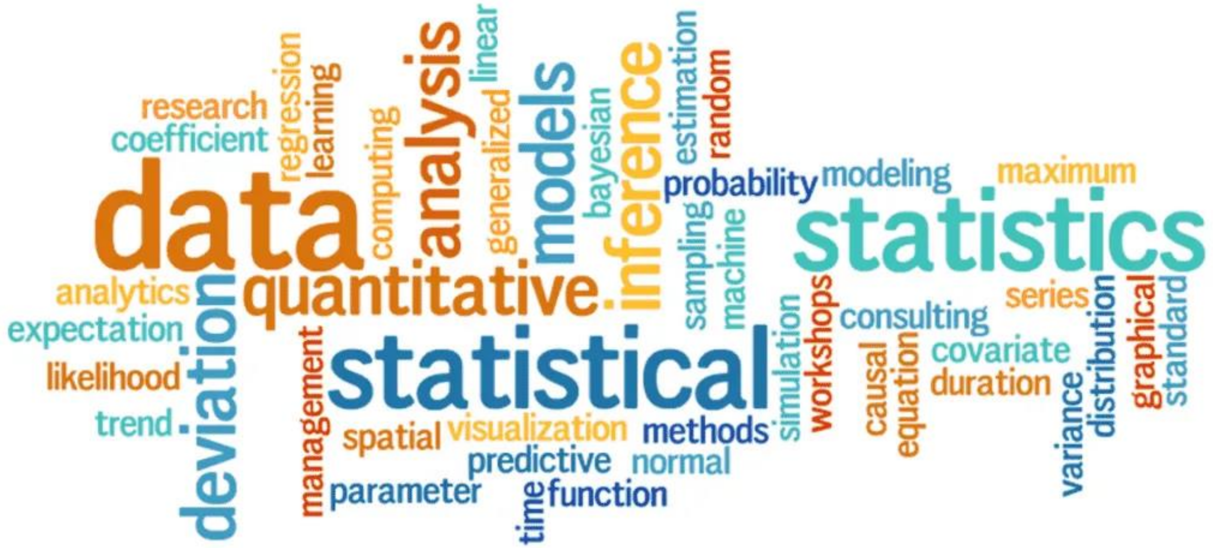

Image from Internet

Day 3: Modeling

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Overview

Time

- 2-hour workshop (45min + 45min + practice/Q&A)

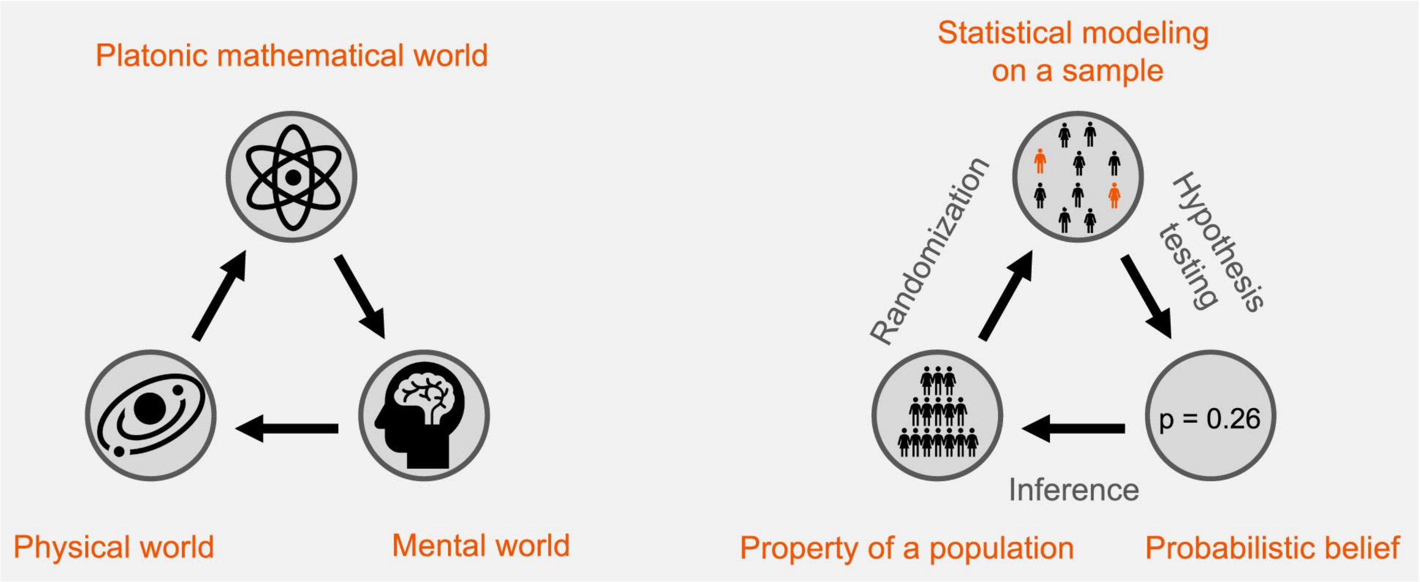
Topics

- ❑ Likelihood and Maximum likelihood estimate
- ❑ Regression techniques
    - ❑ Linear
    - ❑ Logistic
    - ❑ Local
    - ❑ Penalized
- ❑ Model selection
- ❑ Statistical fallacy

Summary – Day1&2

Introduction to probability and statistics

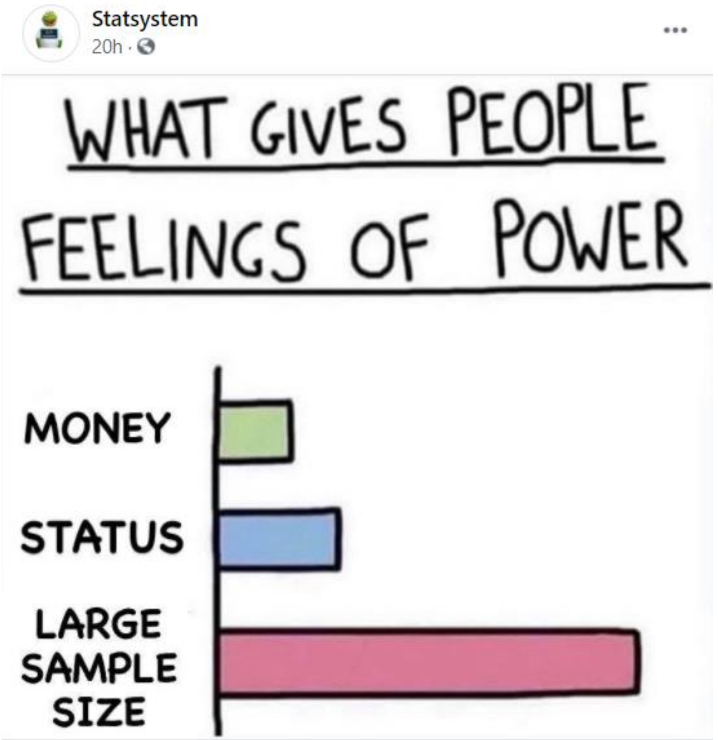
- ❑ Uncertainty
- ❑ Probability
- ❑ Distributions
- ❑ Descriptive statistics
- ❑ Inferential statistics



Summary – Day1&2

Foundations of statistics

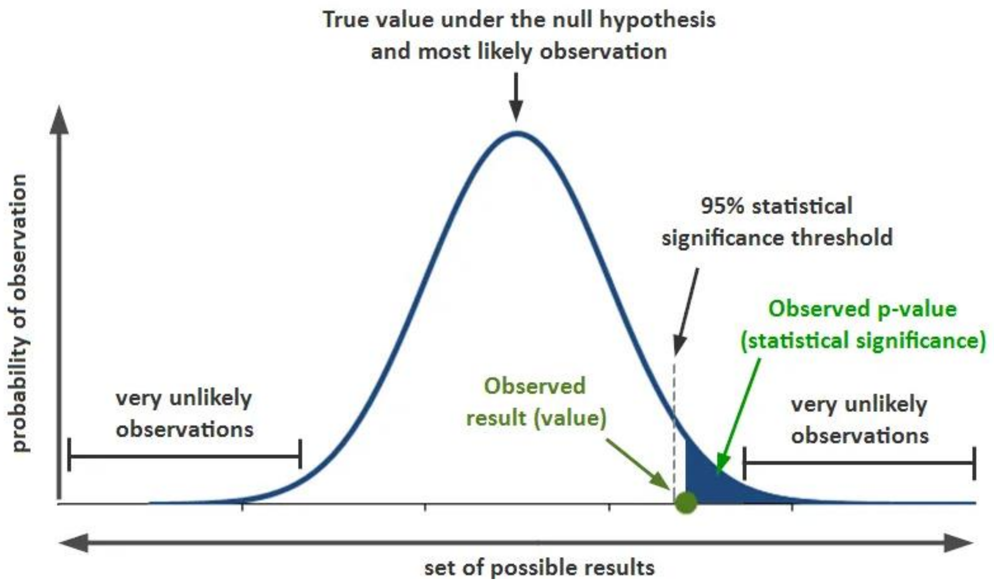
- ❑ Population & Samples
- ❑ Law of Large Numbers (LLN)
- ❑ Central Limit Theorem (CLT)

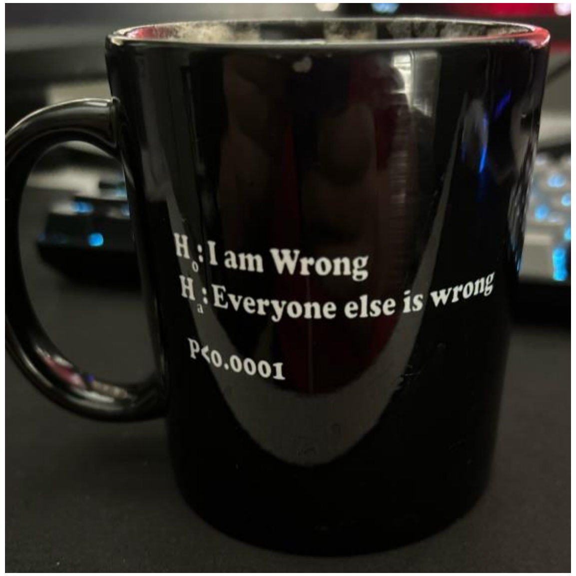


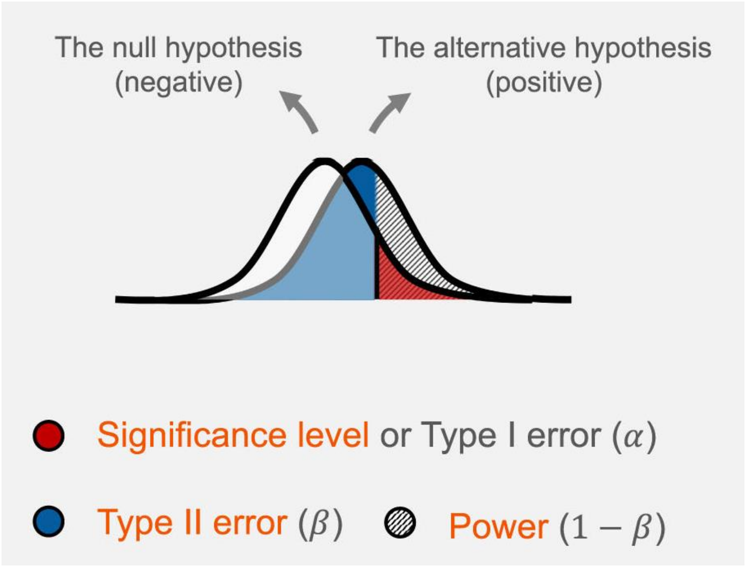
Summary – Day1&2

Hypothesis testing

- ❑ Statistical tests
- ❑ *p*-value
- ❑ Decision errors



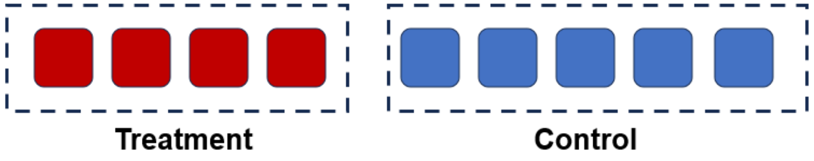


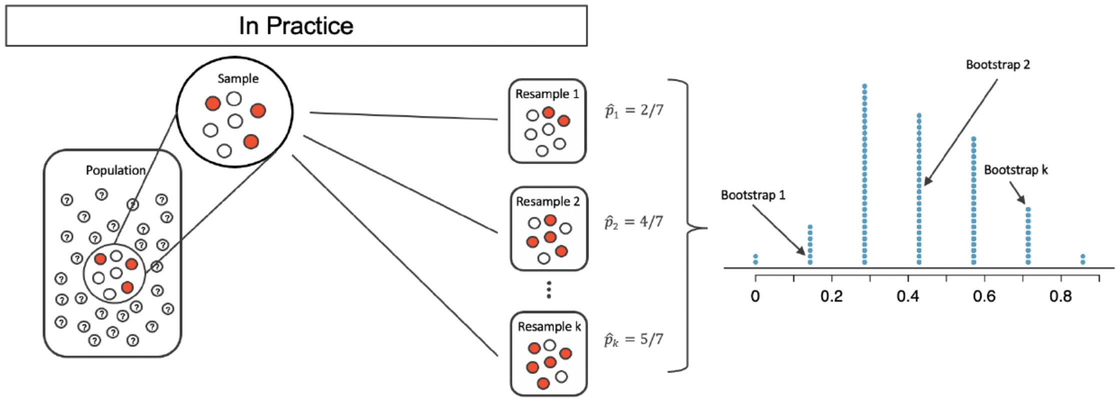


Summary – Day1&2

Computation aided inference

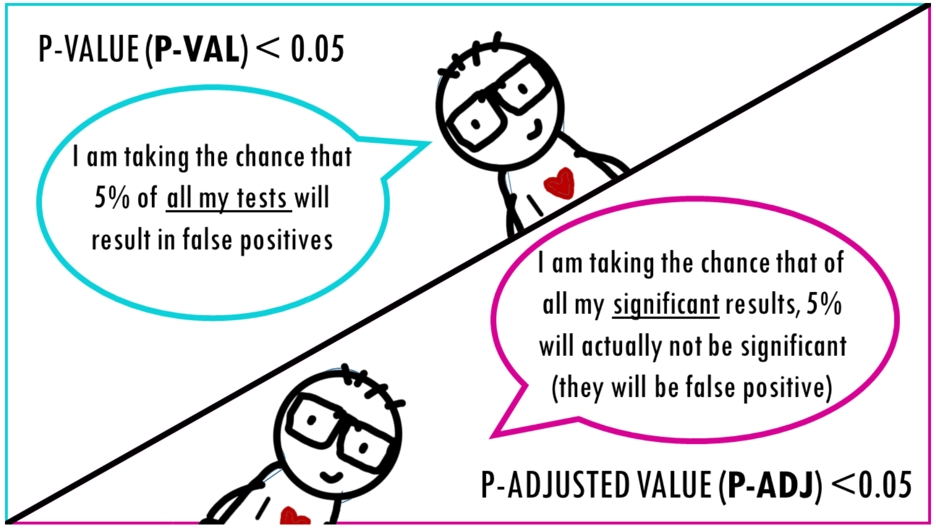
- ❑ Permutation test
- ❑ Bootstrap





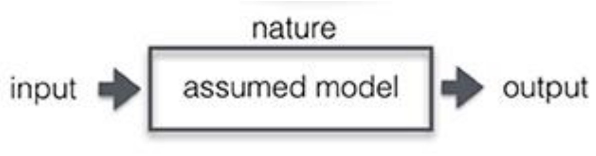
Multiple test correction

- ❑ Bonferroni correction
- ❑ Benjamini-Hochberg

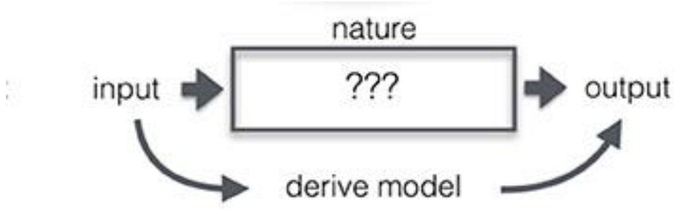


Inference vs. prediction: different focuses

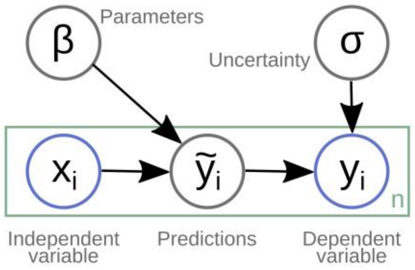
Inference: Understanding relationships, estimating parameters, and testing hypotheses.

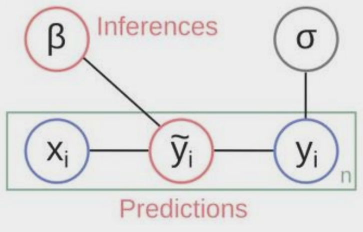
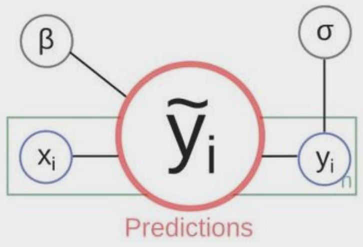


Prediction: : Accurately forecasting or predicting outcomes for new data.

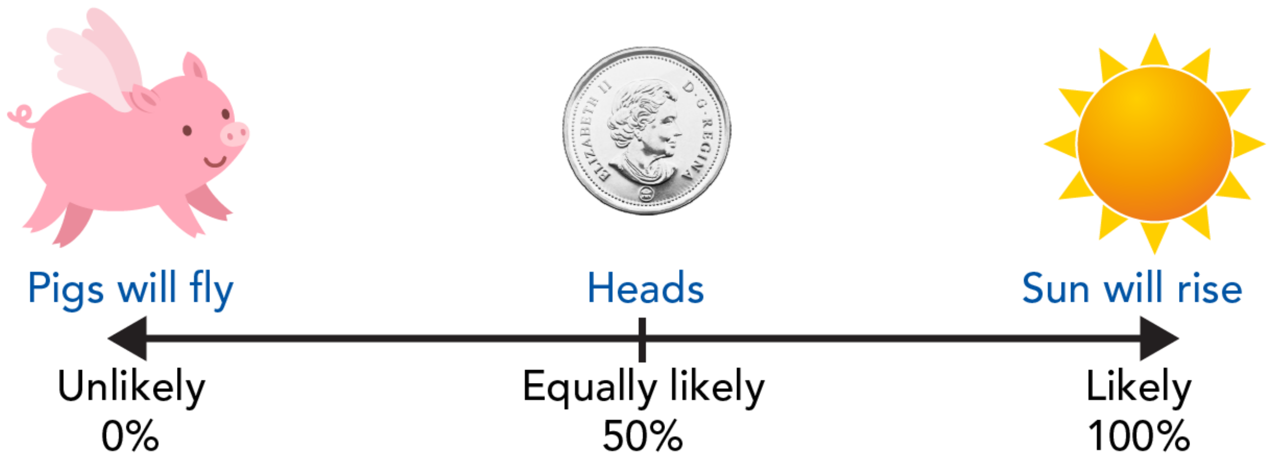


In linear model



	Inference	Prediction
Overview		
Goal	Understanding	Forecasting
Focus	Parameter estimation	Model accuracy
Task	Hypothesis testing	Classification or regression
Evaluation	Statistical significance	Predictive performance (AUC, MSE)

Breiman, Leo. (2001), *Statistical science*
Sanders, N (2019), *Harvard Data Science Review*



Likelihood

"*It is likely that unlikely things should happen*" – Aristotle

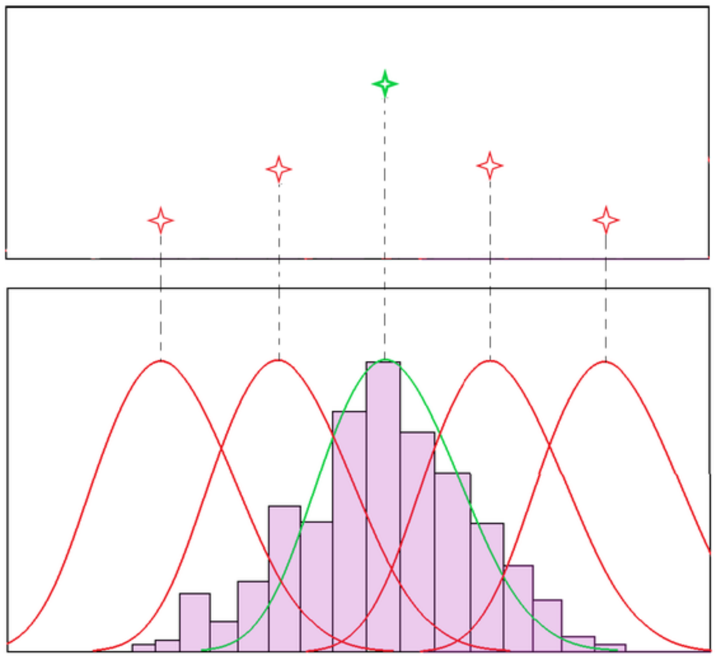
Image from Internet

Consider a toy example

Flip a coin 10 times and record the outcome **D**

All heads

Maximum likelihood estimate plot



Multiple PDFs over the
random sample histogram plot

What's the probability of observing such data when $\theta = 0.5$?

$$\mathrm{P}(\boldsymbol{D} \mid \theta = 0.5) = \left(\frac{1}{2}\right)^{10} < 0.001$$

So, we encounter such a small probability event just by chance?

What if $\theta \neq 0.5$? (we are questioning the fairness of the coin)

Maximum likelihood estimate (MLE)

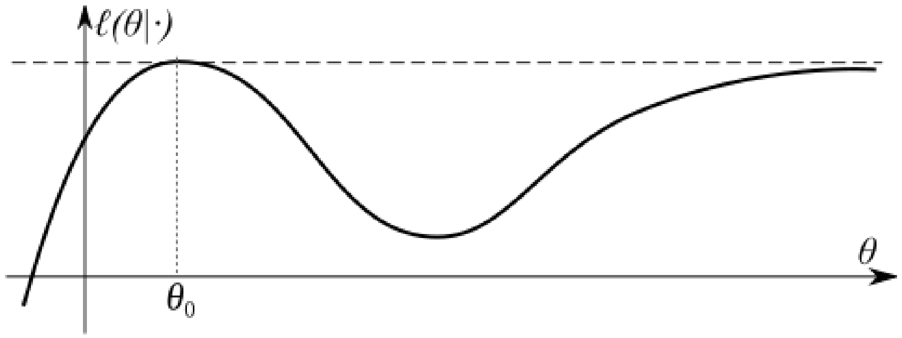
With model parameters $\boldsymbol{\theta}$ and observed data **D**,

Define the likelihood function

$$L(\boldsymbol{\theta}) = L(\boldsymbol{\theta}; \boldsymbol{D}) = \mathrm{f}\,(\mathbf{D} \mid \boldsymbol{\theta})$$

The goal of MLE is to find $\widehat{\boldsymbol{\theta}}$ such that

$$\widehat{\boldsymbol{\theta}} = argmax\ L(\boldsymbol{\theta}; \boldsymbol{D})$$



Ronald Fisher
(1890- 1962)

a genius who almost single-handedly created the foundations for modern statistical science

Likelihood for Frequentist & Bayesian

Probability (mathematics)

$$P(H|D) = \frac{P(D|H)P(H)}{P(D)}$$

Everyone uses Bayes' formula when the prior $P(H)$ is known.

Bayesian path

Frequentist path

Statistics (art)

$$P_{\text{Posterior}}(H|D) = \frac{P(D|H)P_{\text{prior}}(H)}{P(D)}$$

Bayesians require a prior, so they develop one from the best information they have.

Likelihood $L(H;D) = P(D|H)$

Without a known prior frequentists draw inferences from just the likelihood function.

Likelihood-Ratio test (LRT)

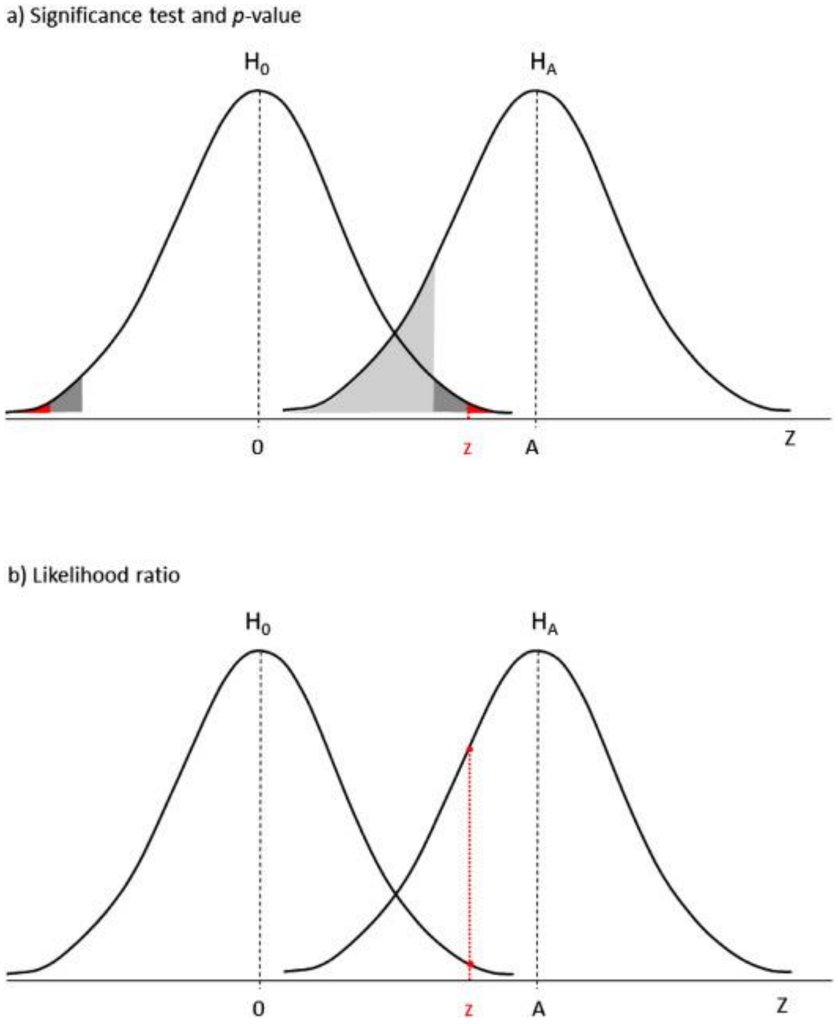
10.21 Definition. *Consider testing*

$$H_0 : \theta \in \Theta_0 \quad \text{versus} \quad H_1 : \theta \notin \Theta_0.$$

The **likelihood ratio statistic** *is*

$$\lambda = 2 \log \left(\frac{\sup_{\theta \in \Theta} \mathcal{L}(\theta)}{\sup_{\theta \in \Theta_0} \mathcal{L}(\theta)} \right) = 2 \log \left(\frac{\mathcal{L}(\widehat{\theta})}{\mathcal{L}(\widehat{\theta}_0)} \right)$$

where $\widehat{\theta}$ is the MLE *and $\widehat{\theta}_0$ is the* MLE *when θ is restricted to lie in Θ_0.*



When H_0 is true, λ follows a chi-square distribution

$$\lambda \sim \chi^2_d$$

Where d is the dimension difference between H_0 and H_1

(**Nyeman-Pearson Lemma further proved it's the most powerful test**)

Let’s do some practice!

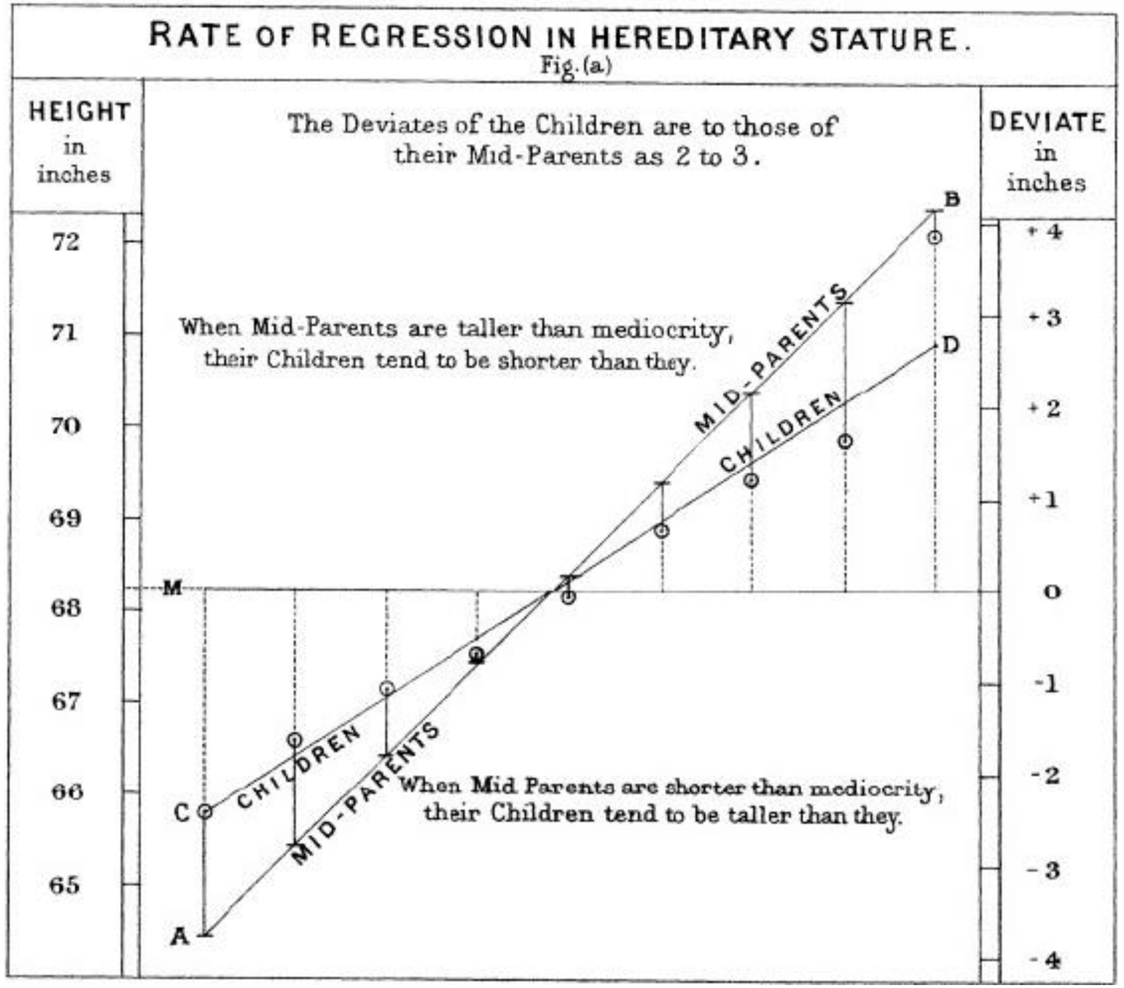
- git clone https://github.com/wbvguo/qcbio-Intro2ModernStats.git

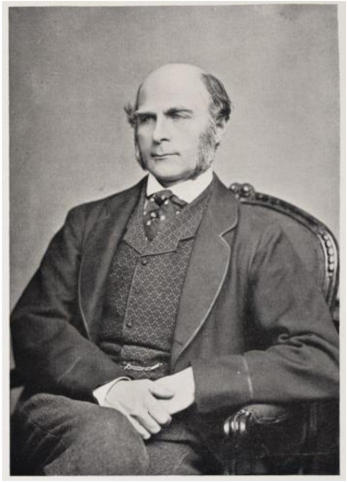
Regression

Chaos finds order in the mean.

The history of regression

“the average regression of the offspring is a constant fraction of their respective mid-parental deviations”





Francis Galton
(1822-1911)

Regression towards the mean

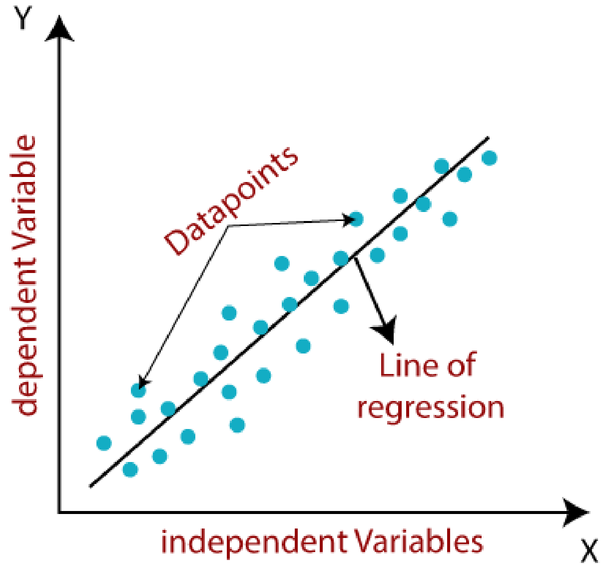
Simple linear regression

Dependent Variable; Population Y intercept; Population Slope Coefficient; Independent Variable; Random Error term

$$Y_i = \underbrace{\beta_0 + \beta_1 X_i}_{\text{Linear component}} + \underbrace{\varepsilon_i}_{\text{Random Error component}}$$

How can we estimate β_0 and β_1?

- ❑ Ordinary Least Square (OLS)
- ❑ Maximum Likelihood Estimate (MLE)



OLS derivation

Rational: minimize the fitting error (loss function)

Define the loss

$$\mathrm{RSS}(\beta_0, \beta_1) = \sum_{i=1}^{n} \varepsilon_i^2 = \sum_{i=1}^{n} (y_i - \beta_0 - \beta_1 x_i)^2 \ .$$

Take the derivative and set to 0

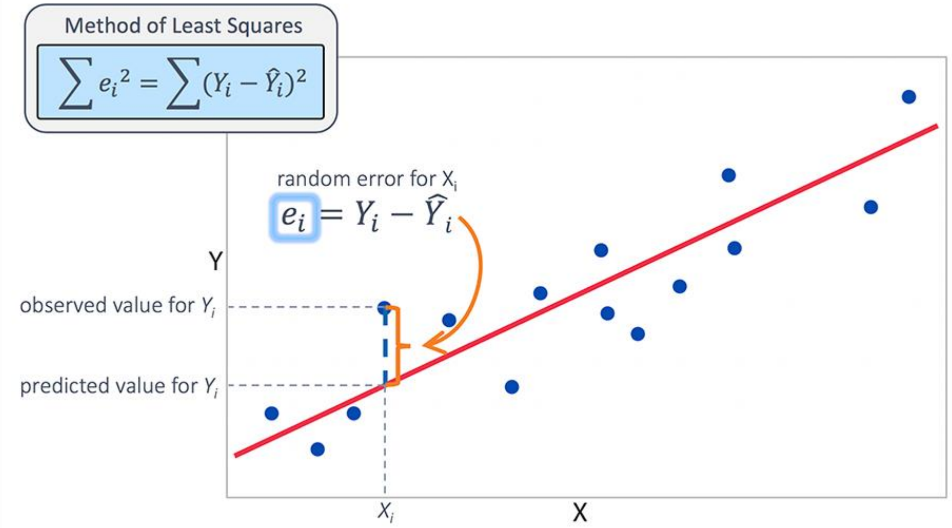
$$0 = -2 \sum_{i=1}^{n} (y_i - \hat{\beta}_0 - \hat{\beta}_1 x_i)$$

$$0 = -2 \sum_{i=1}^{n} (x_i y_i - \hat{\beta}_0 x_i - \hat{\beta}_1 x_i^2)$$

Solve the equation

$$\left.\begin{aligned} \hat{\beta}_0 &= \bar{y} - \hat{\beta}_1 \bar{x} \\ \hat{\beta}_1 &= \frac{s_{xy}}{s_x^2} = \frac{\frac{1}{n-1}\sum_{i=1}^{n}(x_i - \bar{x})(y_i - \bar{y})}{\frac{1}{n-1}\sum_{i=1}^{n}(x_i - \bar{x})^2} \end{aligned}\right\} \quad \hat{\beta} = (\mathbf{X}^{\mathrm{T}}\mathbf{X})^{-1}\mathbf{X}^{\mathrm{T}}\mathbf{Y}$$

where $\mathbf{X} = \begin{bmatrix} 1 & x_1 \\ \vdots & \vdots \\ 1 & x_n \end{bmatrix} \in \mathbb{R}^{n\times 2}$



MLE derivation

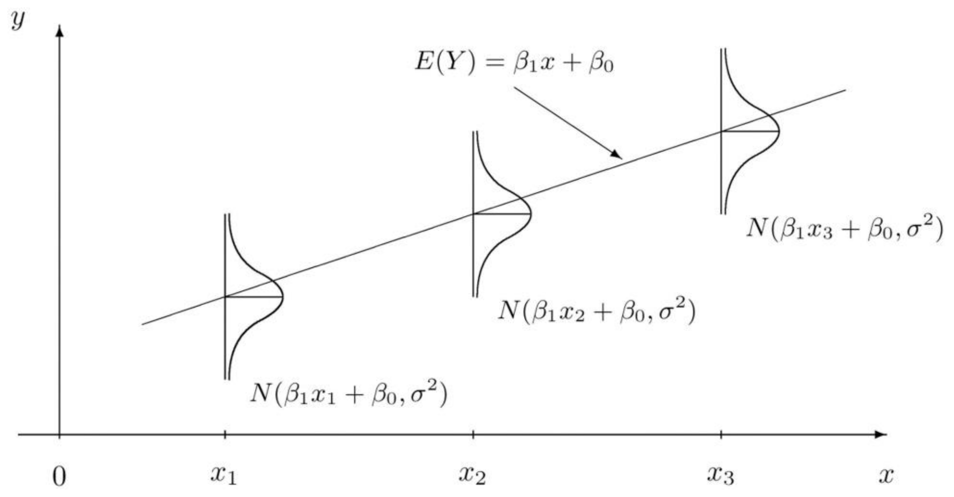
$$y = \beta_0 + \beta_1 x + \epsilon$$

$$\epsilon \sim N(0, \delta^2)$$

Rational: maximize the likelihood

$$p(y|\beta_0, \beta_1, \sigma^2) = \prod_{i=1}^{n} p(y_i|\beta_0, \beta_1, \sigma^2)$$

$$= \frac{1}{\sqrt{(2\pi\sigma^2)^n}} \cdot \exp\left[-\frac{1}{2\sigma^2}\sum_{i=1}^{n}(y_i - \beta_0 - \beta_1 x_i)^2\right]$$



Log-Likelihood:

$$\mathrm{LL}(\beta_0, \beta_1, \sigma^2) = \log p(y|\beta_0, \beta_1, \sigma^2)$$

$$= -\frac{n}{2}\log(2\pi) - \frac{n}{2}\log(\sigma^2) - \frac{1}{2\sigma^2}\sum_{i=1}^{n}(y_i - \beta_0 - \beta_1 x_i)^2$$

Take the derivative w.r.t each parameter and set to 0

$$\hat{\beta}_0 = \bar{y} - \hat{\beta}_1 \bar{x}$$

$$\hat{\beta}_1 = \frac{s_{xy}}{s_x^2}$$

$$\hat{\sigma}^2 = \frac{1}{n}\sum_{i=1}^{n}(y_i - \hat{\beta}_0 - \hat{\beta}_1 x_i)^2$$

OLS and MLE are equivalent in this setting

Inference

$$y = \beta_0 + \beta_1 x + \epsilon$$

$$\epsilon \sim N(0, \delta^2)$$

Since $\hat{\beta} = (\mathbf{X}^{\mathrm{T}}\mathbf{X})^{-1}\mathbf{X}^{\mathrm{T}}\mathbf{Y}$, we can derive $\hat{\beta} \sim \mathcal{N}(\beta, \sigma^2(\mathbf{X}^{\mathrm{T}}\mathbf{X})^{-1})$

Now, we have estimates $\hat{\beta}$ from the data, so we can test them

Hypothesis testing:

$$H_0 : \beta_j = 0; \quad H_1 : \beta_j \neq 0$$

The t-statistic:

$$T = \frac{\hat{\beta}_j}{\sqrt{\widehat{\mathrm{Var}}(\hat{\beta}_j)}} = \frac{\hat{\beta}_j}{\hat{\sigma}\sqrt{j^{th} \text{ diagonal entry of } (\mathbf{X}^{\mathrm{T}}\mathbf{X})^{-1}}}$$

For the denominator, we use the *plug-in estimator* (replacing the true value by the estimator).

Prediction

After we obtain the estimator, we can use it to predict for new values

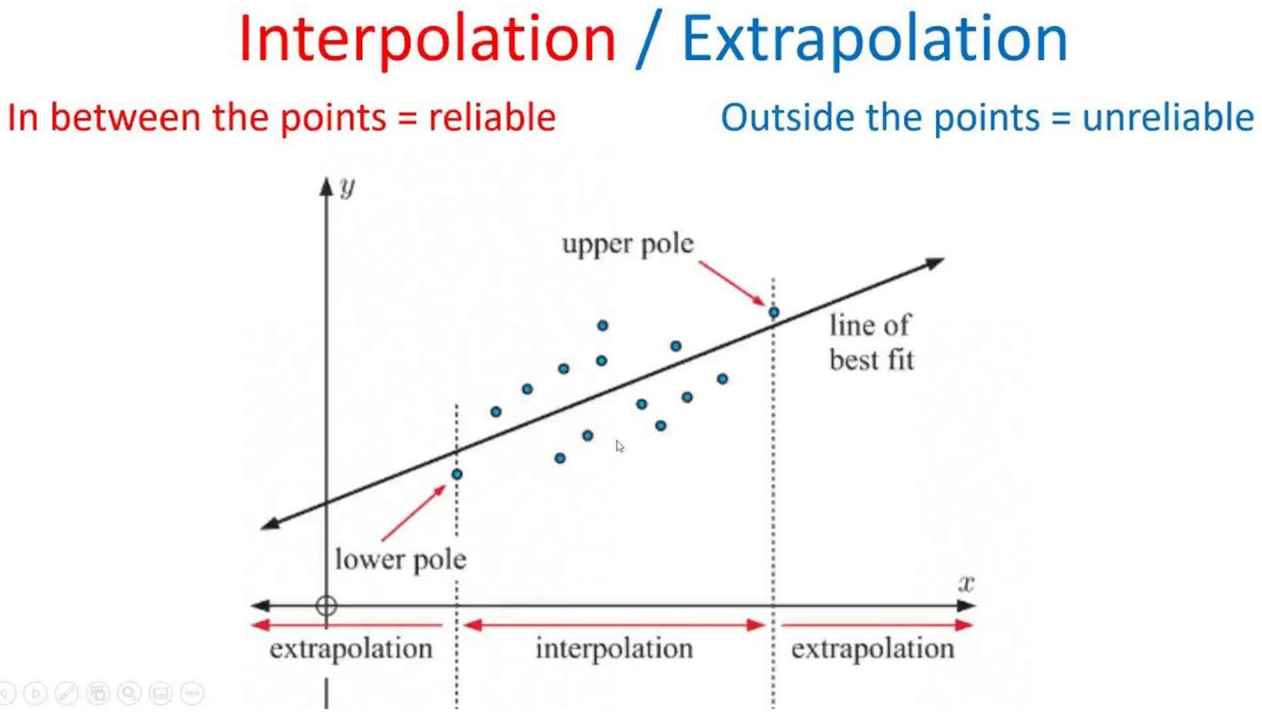
$$\hat{y}_i = \hat{\beta}_0 + \hat{\beta}_1 x_i$$

Residual:

$$e_i = y_i - \hat{y}_i$$

Coefficient of determination:

$$R^2 = \frac{SSR}{SST} = \frac{\sum_{i=1}^{n}(\hat{y}_i - \bar{y})^2}{\sum_{i=1}^{n}(y_i - \bar{y})^2} = r^2$$



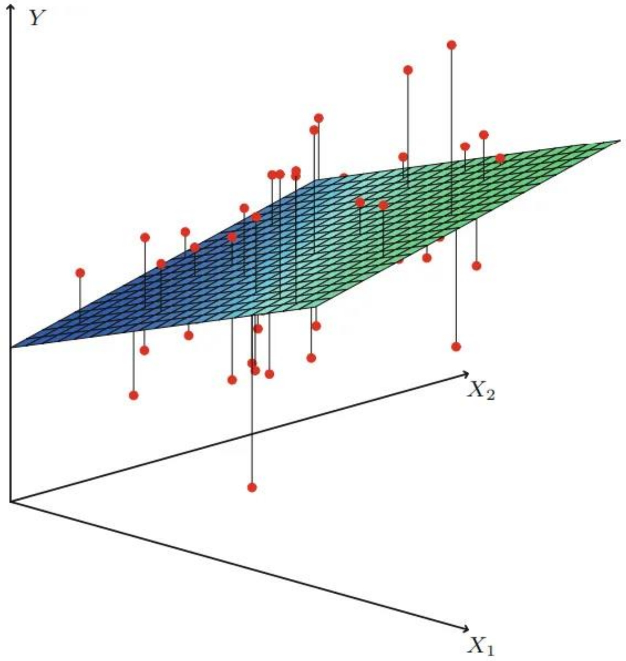
$$r = \frac{\sum_{i=1}^{n}(X_i - \bar{X})(Y_i - \bar{Y})}{\sqrt{\sum_{i=1}^{n}(X_i - \bar{X})^2 \sum_{i=1}^{n}(Y_i - \bar{Y})^2}}$$

The sample correlation

Multiple regression

$$y = \beta_0 + \beta_1 x_1 + \beta_2 x_2 + \cdots + \beta_p x_p + \epsilon$$

$$\epsilon \sim N(0, \delta^2)$$



Parameter estimation:

$$\hat{\beta} = (\mathbf{X}^{\mathrm{T}}\mathbf{X})^{-1}\mathbf{X}^{\mathrm{T}}\mathbf{Y}$$

Inference

$$\hat{\beta} \sim \mathcal{N}(\beta, \sigma^2(\mathbf{X}^{\mathrm{T}}\mathbf{X})^{-1})$$

Consistent with the simple linear regression

Question: what would happen when p >> n ?

Logistic regression

$$\mathrm{logit}(p_i) = \beta_0 + \sum_{j=1}^{k} \beta_j x_{ij}$$

$$Y_i | X_i = x_i \sim \mathrm{Bernoulli}(p_i)$$

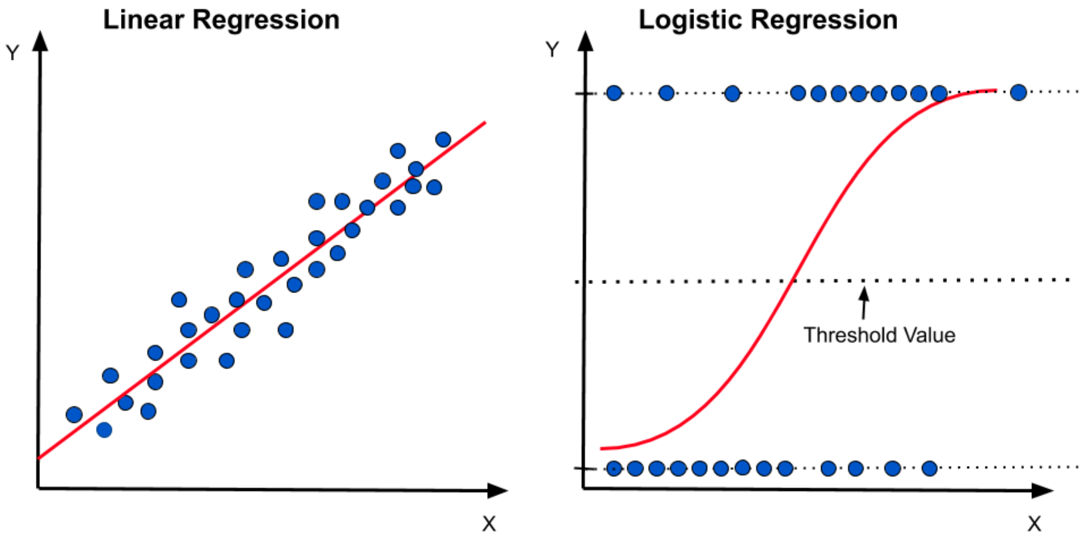
$$\mathrm{logit}(p) = \log\left(\frac{p}{1-p}\right)$$

Logit transformation

Likelihood:

$$\mathcal{L}(\beta) = \prod_{i=1}^{n} p_i(\beta)^{Y_i}(1 - p_i(\beta))^{1-Y_i}$$

MLE can be obtained using numerical approach



Local regression

LOcal regrESSion (LOESS): non-parametric

Model

$$Y_i = \mu(x_i) + \epsilon_i$$

$$\mu(x_i) \approx \beta_0 + \beta_1(x_i - x) + \ldots + \beta_p(x_i - x)^p$$

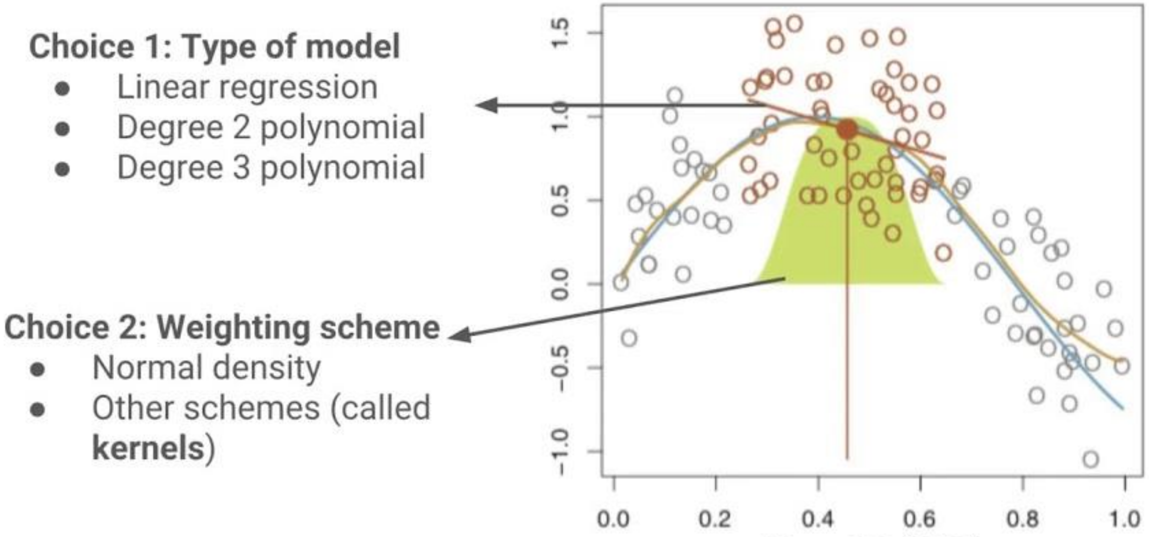


Figure 7.9 (ISLR)

Loss function

$$\sum_{i=1}^{n} w_i(x)(Y_i - \beta_0 - \beta_1(x_i - x) - \ldots - \beta_p(x_i - x)^p)^2$$

Where $w_i(x) = W\left(\frac{x_i - x}{h}\right)$ is a weight function (kernel)

Overfitting: Von Neumann's elephant

"I remember my friend Johnny von Neumann used to say, with four parameters I can fit an elephant, and with five I can make him wiggle his trunk." - Enrico Fermi

John von Neumann
(1903-1957)

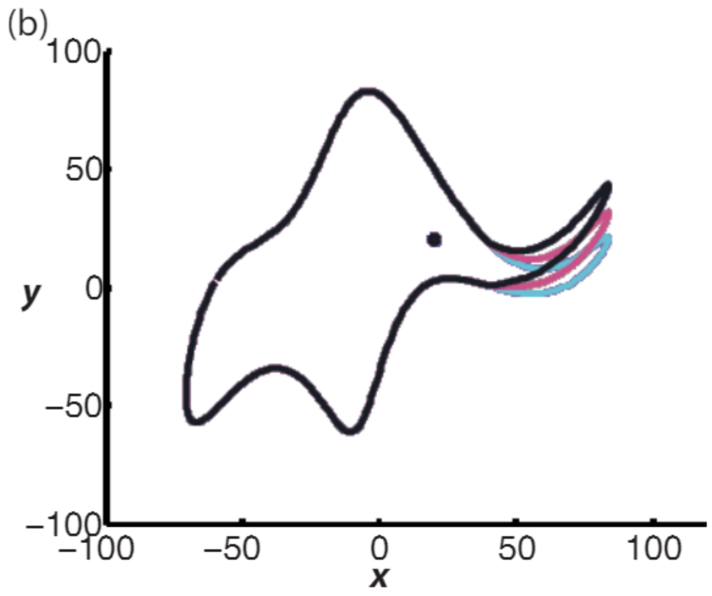


Table I. The five complex parameters $p_1, \ldots, p_5$ that encode the elephant including its wiggling trunk.

Parameter	Real part	Imaginary part
$p_1 = 50 - 30i$	$B_1^x = 50$	$B_1^y = -30$
$p_2 = 18 + 8i$	$B_2^x = 18$	$B_2^y = 8$
$p_3 = 12 - 10i$	$A_3^x = 12$	$B_3^y = -10$
$p_4 = -14 - 60i$	$A_5^x = -14$	$A_1^y = -60$
$p_5 = 40 + 20i$	Wiggle coeff. $= 40$	$x_{eye} = y_{eye} = 20$

(Mayer et al. *Am. J. Phys, 2010*)

Penalized regression

- Lasso (L1 penalty)

$$J(\boldsymbol{\theta}) = \mathrm{MSE}(\boldsymbol{\theta}) + \alpha \sum_{i=1}^{n} |\theta_i|$$

- Ridge (L2 penalty)

$$J(\boldsymbol{\theta}) = \mathrm{MSE}(\boldsymbol{\theta}) + \alpha \frac{1}{2} \sum_{i=1}^{n} {\theta_i}^2$$

- Elastic-net

$$J(\boldsymbol{\theta}) = \mathrm{MSE}(\boldsymbol{\theta}) + r\alpha \sum_{i=1}^{n} |\theta_i| + \frac{1-r}{2} \alpha \sum_{i=1}^{n} {\theta_i}^2$$

This forces the learning algorithm to not only fit the data but also keep the model weights as small as possible!

Penalized regression

- Lasso (L1 penalty)

$$J(\boldsymbol{\theta}) = \mathrm{MSE}(\boldsymbol{\theta}) + \alpha \sum_{i=1}^{n} |\theta_i|$$

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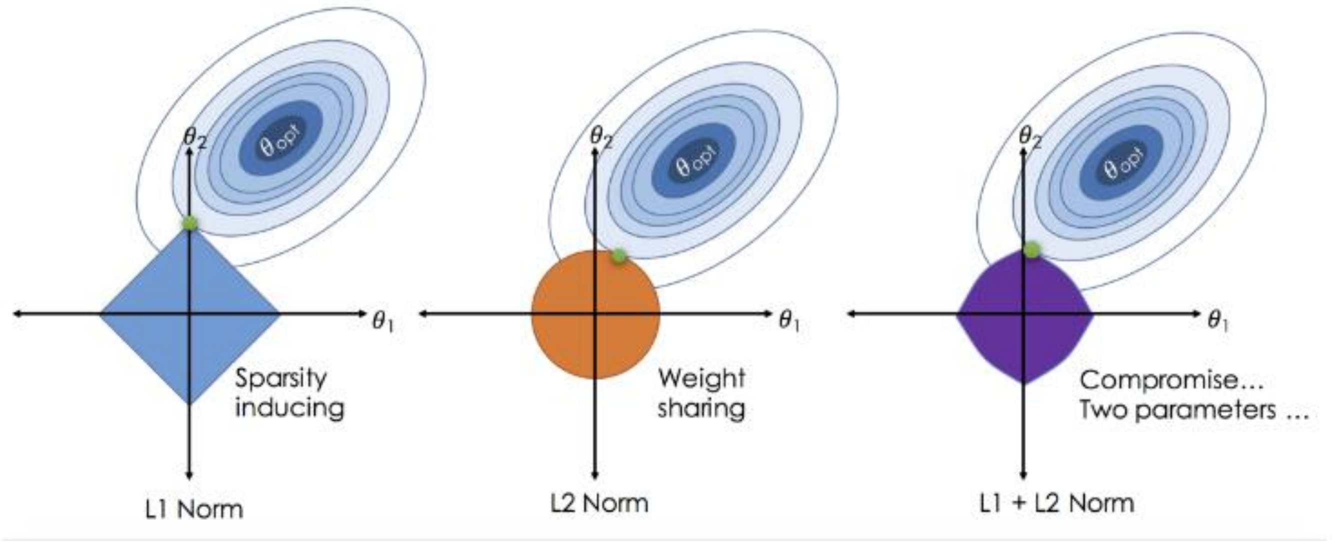
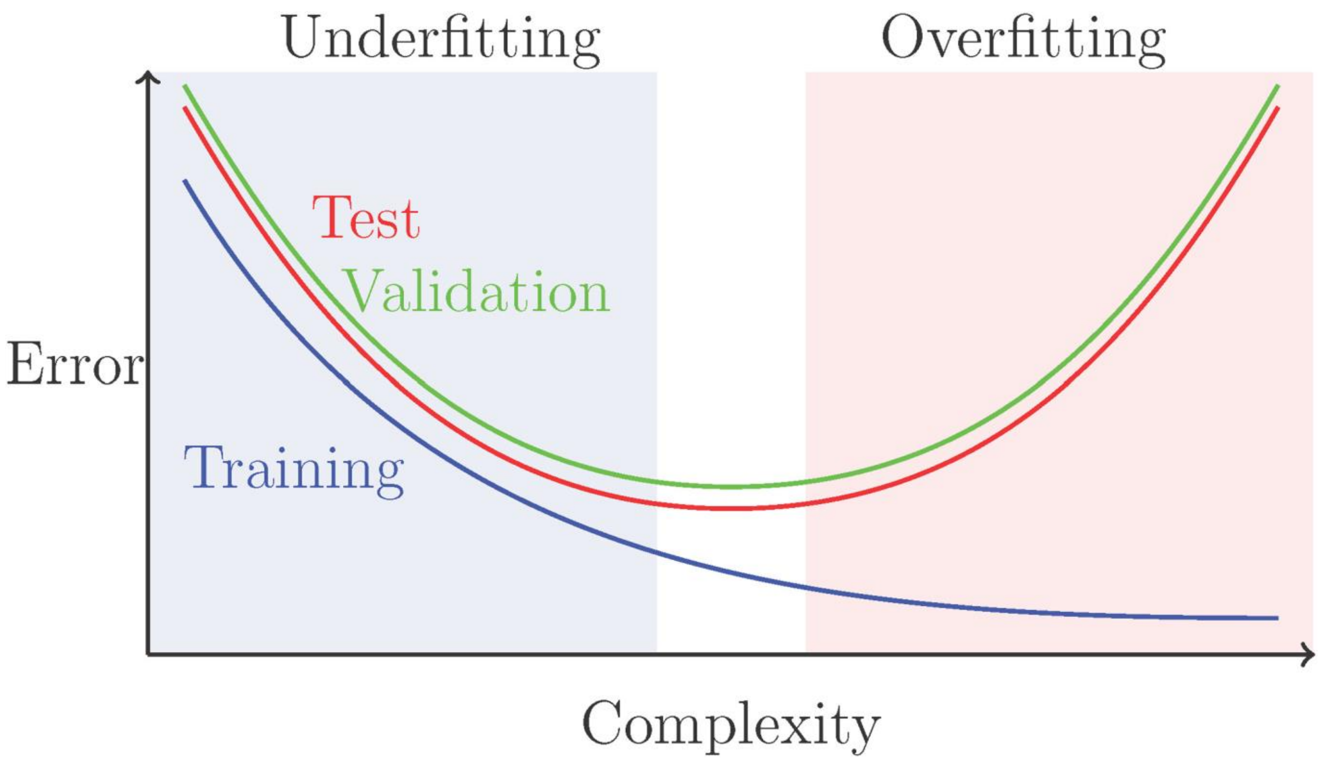
$$J(\boldsymbol{\theta}) = \mathrm{MSE}(\boldsymbol{\theta}) + r\alpha \sum_{i=1}^{n} |\theta_i| + \frac{1-r}{2} \alpha \sum_{i=1}^{n} {\theta_i}^2$$

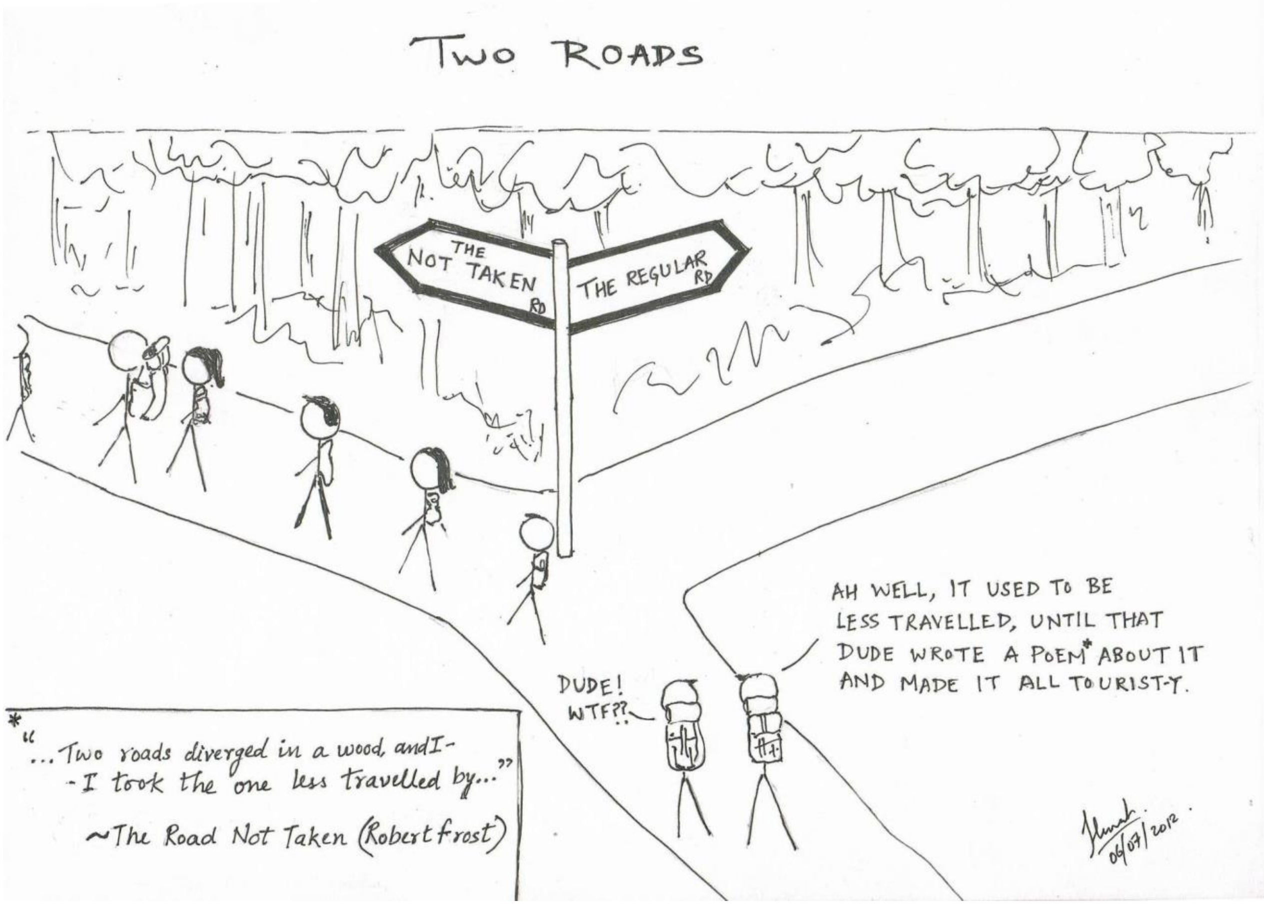


https://towardsdatascience.com/from-linear-regression-to-ridge-regression-the-lasso-and-the-elastic-net-4eaecaf5f7e6

The need for penalization



Model selection



"The choices we make dictate the life we lead. " – William Shakespeare

Model selection in history

In modeling planet movement

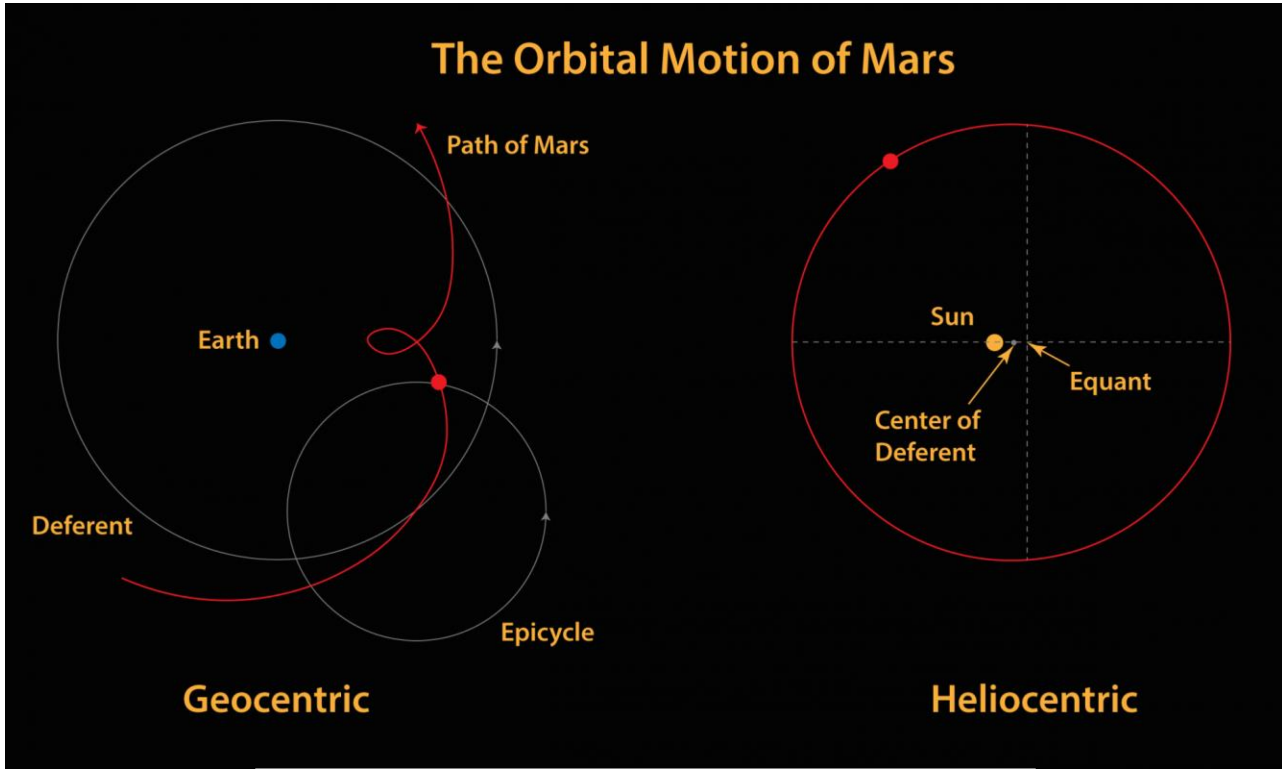
- ❑ Apollonius of Perga: epicycle

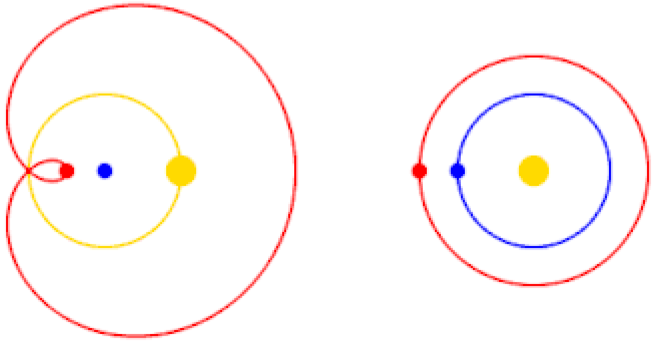
$$z(t) = \sum_{k=1}^{d} r_k e^{i\omega_k t}$$

- ❑ Johannes Kepler: elliptical orbits

$$r = \frac{a(1-e^2)}{1 + e\cos\theta}$$

Occam's Razor: favor parsimonious model





Model selection – probabilistic approach

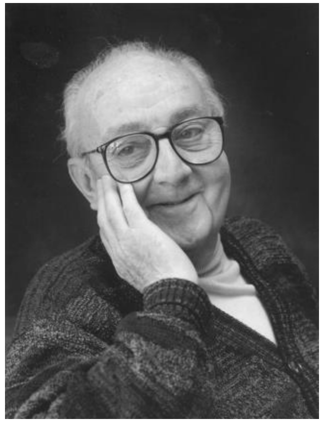
trade-off between the goodness of fit of the model and the simplicity of the model

- Akaike information criterion (AIC)

$$\mathrm{AIC} = 2k - 2\ln(\hat{L})$$

- Bayesian information criterion (BIC)

$$\mathrm{BIC} = k\ln(n) - 2\ln(\widehat{L}).$$



George Box
(1919-2013)

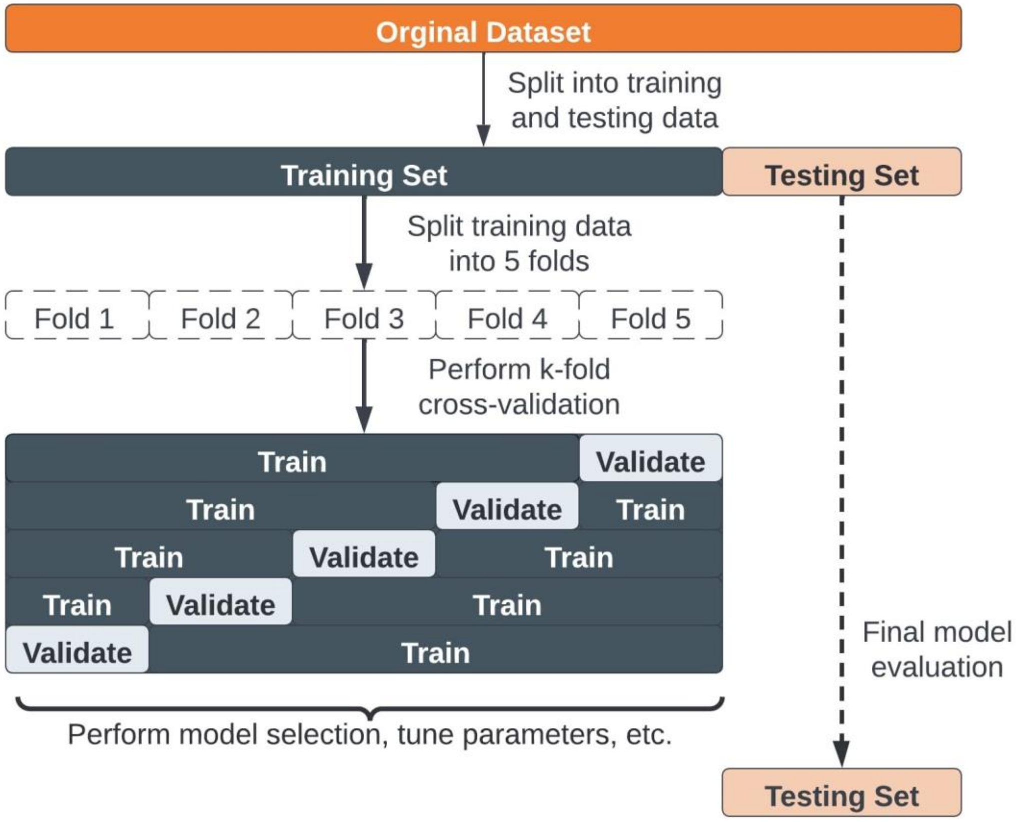
“All models are wrong, but some are useful.”

Model selection – resampling approach

Cross-validation (CV)

Data split

- A training set is used to train the machine learning model(s) during development.
- A validation set is used to estimate the generalization error of the model created from the training set for the purpose of model selection.
- A test set is used to estimate the generalization error of the final model.

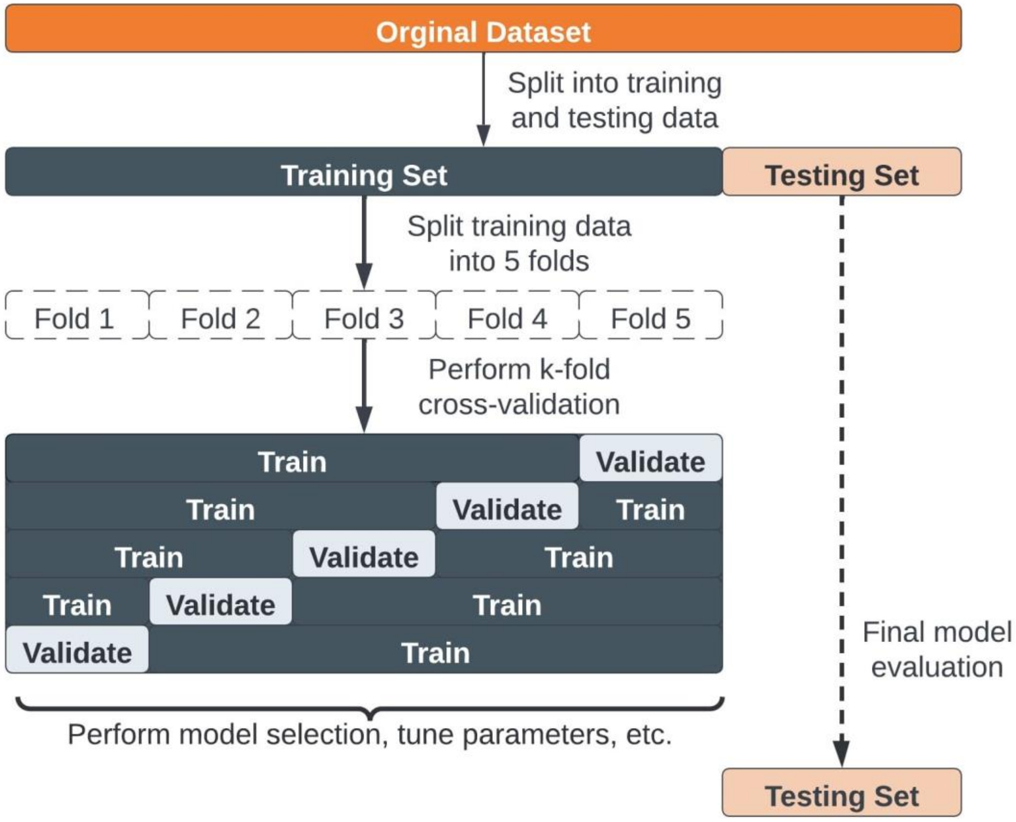


Model selection – resampling approach

Cross-validation (CV)

Procedure

- ❑Split data into portions.
- ❑Train model on a subset of the portions.
- ❑Test model on the remaining subsets of the data.
- ❑Repeat steps 2-3 until the model has been trained and tested on the entire dataset.
- ❑Average the model performance across all iterations of testing to get the total model performance.



Statistical fallacy

May you have a clear mind and sharp eyes.

Flaw of averages

The average can be a **poor representation** for the samples (due to skewness, outliers, etc.)

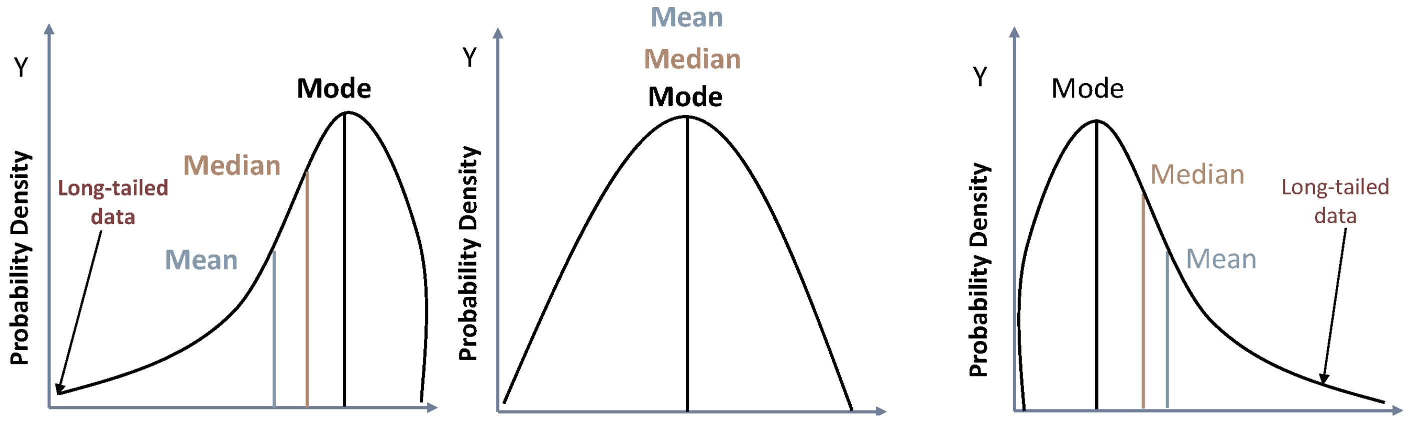


Photo with Dr. Heng Li
RECOMB 2024@MIT

Before learning statistics:

- I am standing next to a guy with citations more than 250,000 🥹

After learning statistics:

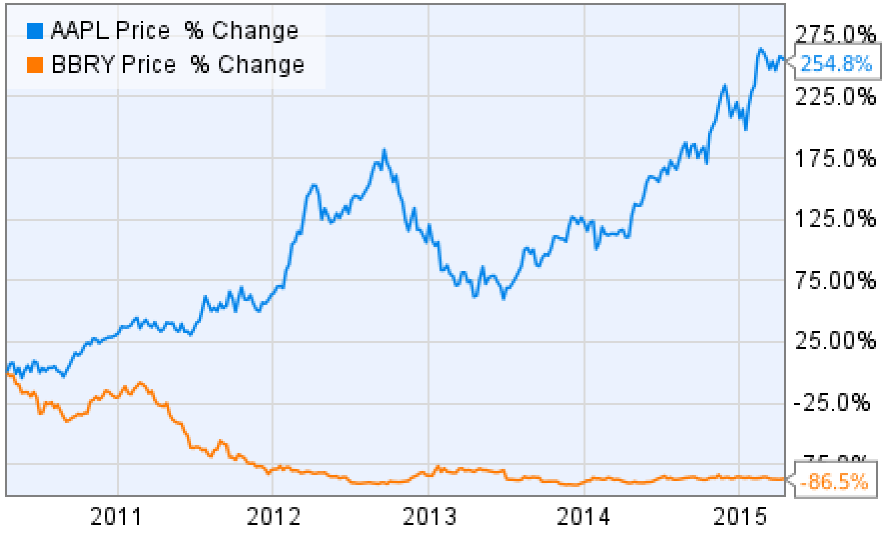
- Our **average** citations are more than 125,000! 😎

Stability isn’t always good

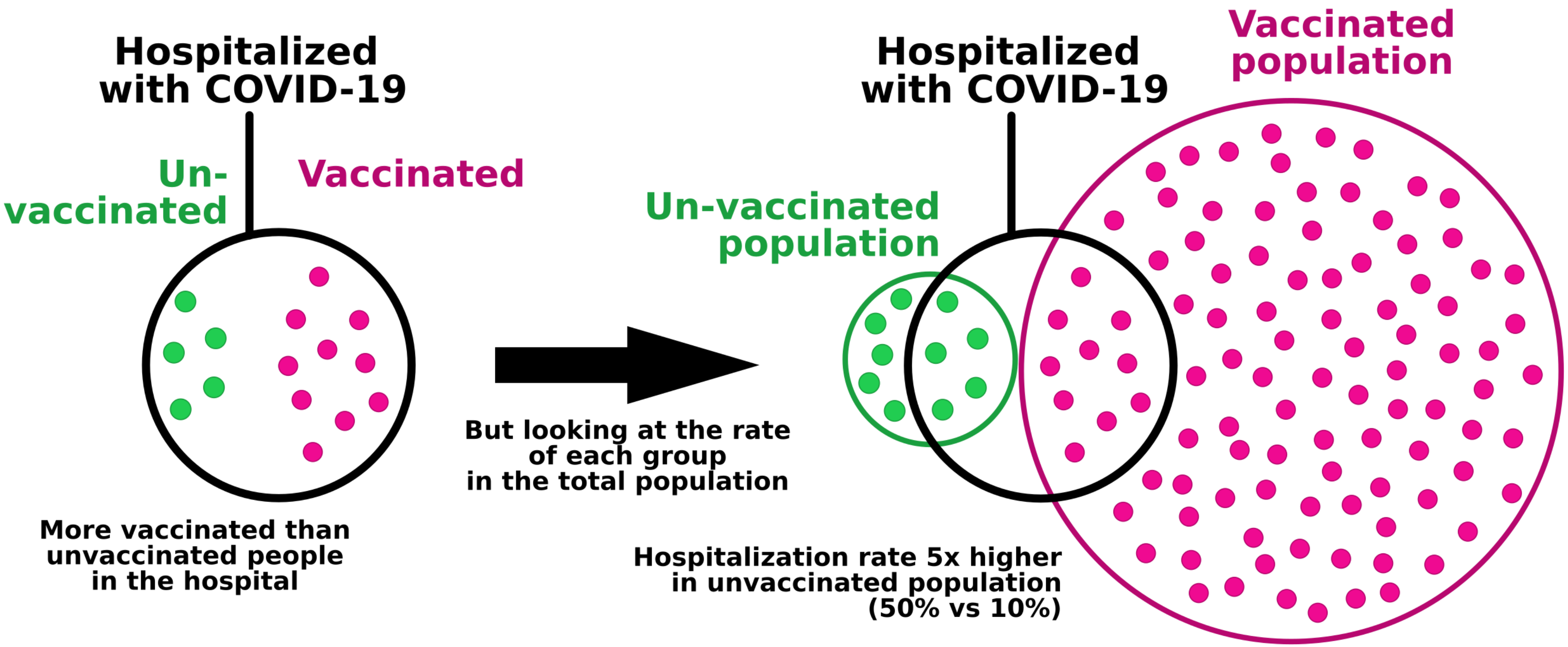
Stability only reflects **variation**, not **mean**

His condition is very stable

- He can be just fine and recovering smoothly
- He can be seriously ill and in ICU every day

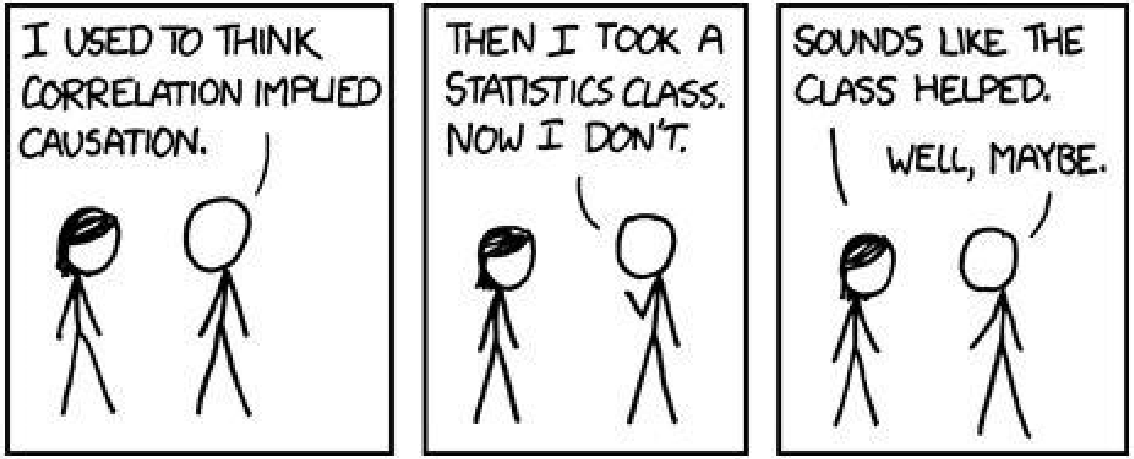


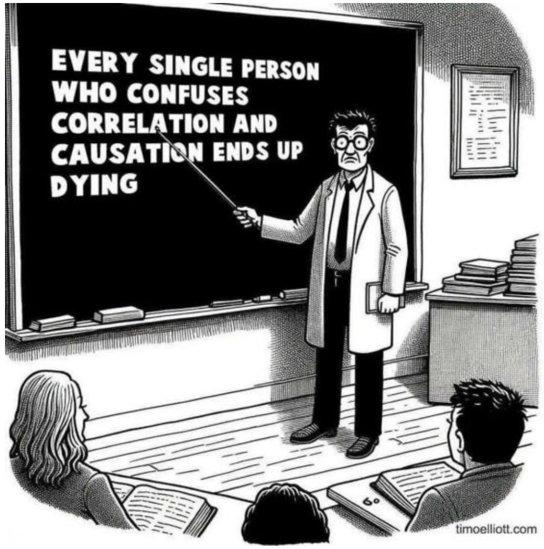
Base rate fallacy

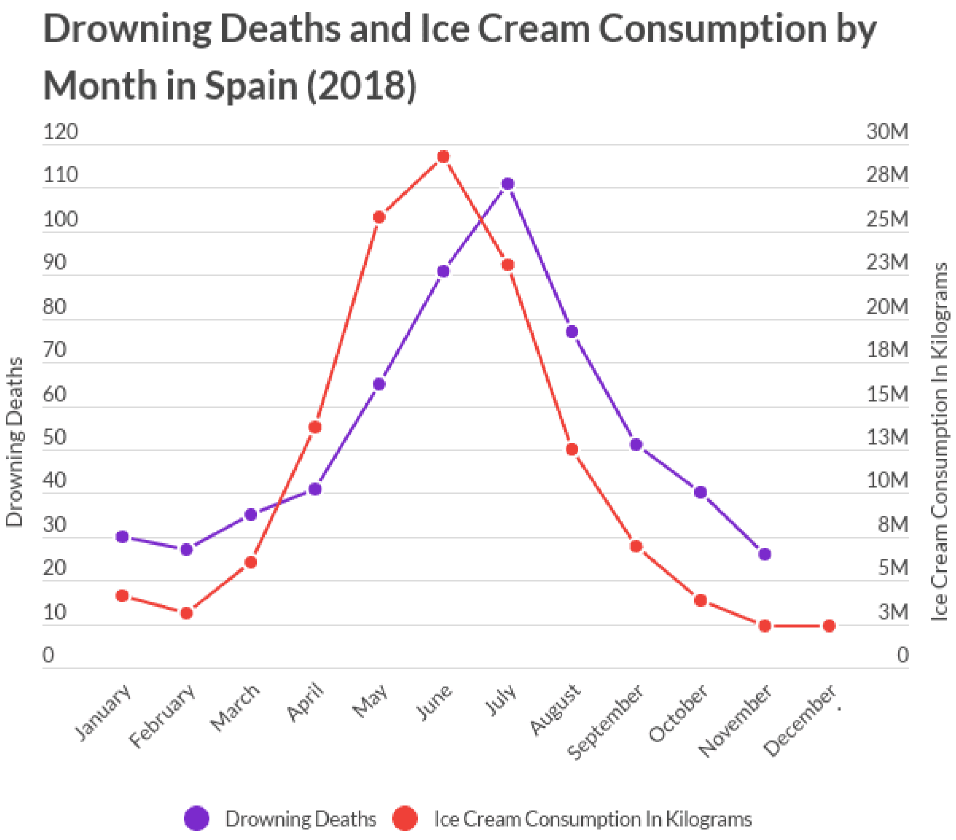


Also related to False positive paradox

Correlation doesn’t imply causation

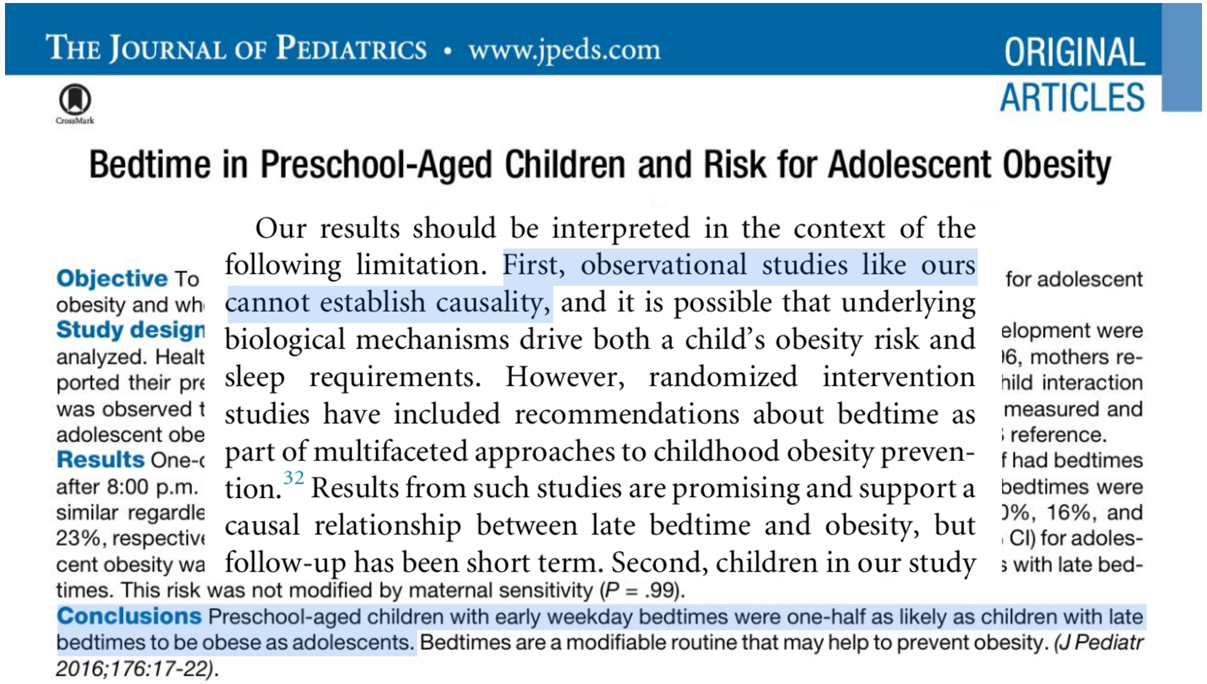






Statista (2020)

Correlation doesn't imply causation (cont'd)


THE JOURNAL OF PEDIATRICS • www.jpeds.com

ORIGINAL ARTICLES

CrossMark

Bedtime in Preschool-Aged Children and Risk for Adolescent Obesity

Objective To ... for adolescent obesity and wh...

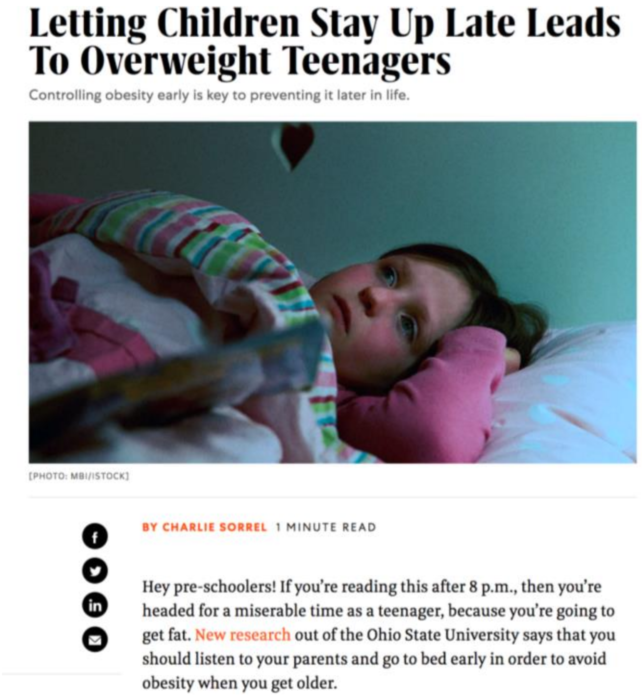
Study design ... elopment were analyzed. Healt... 6, mothers reported their pre... hild interaction was observed t... measured and adolescent obe... reference.

Results One-... f had bedtimes after 8:00 p.m. ... bedtimes were similar regardle... 0%, 16%, and 23%, respectiv... CI) for adolescent obesity wa... s with late bedtimes. This risk was not modified by maternal sensitivity (P = .99).

Conclusions Preschool-aged children with early weekday bedtimes were one-half as likely as children with late bedtimes to be obese as adolescents. Bedtimes are a modifiable routine that may help to prevent obesity. (*J Pediatr 2016;176:17-22*).

Our results should be interpreted in the context of the following limitation. First, observational studies like ours cannot establish causality, and it is possible that underlying biological mechanisms drive both a child's obesity risk and sleep requirements. However, randomized intervention studies have included recommendations about bedtime as part of multifaceted approaches to childhood obesity prevention.[32] Results from such studies are promising and support a causal relationship between late bedtime and obesity, but follow-up has been short term. Second, children in our study

What research article says


Letting Children Stay Up Late Leads To Overweight Teenagers

Controlling obesity early is key to preventing it later in life.

[PHOTO: MBI/ISTOCK]

BY CHARLIE SORREL 1 MINUTE READ

Hey pre-schoolers! If you're reading this after 8 p.m., then you're headed for a miserable time as a teenager, because you're going to get fat. New research out of the Ohio State University says that you should listen to your parents and go to bed early in order to avoid obesity when you get older.

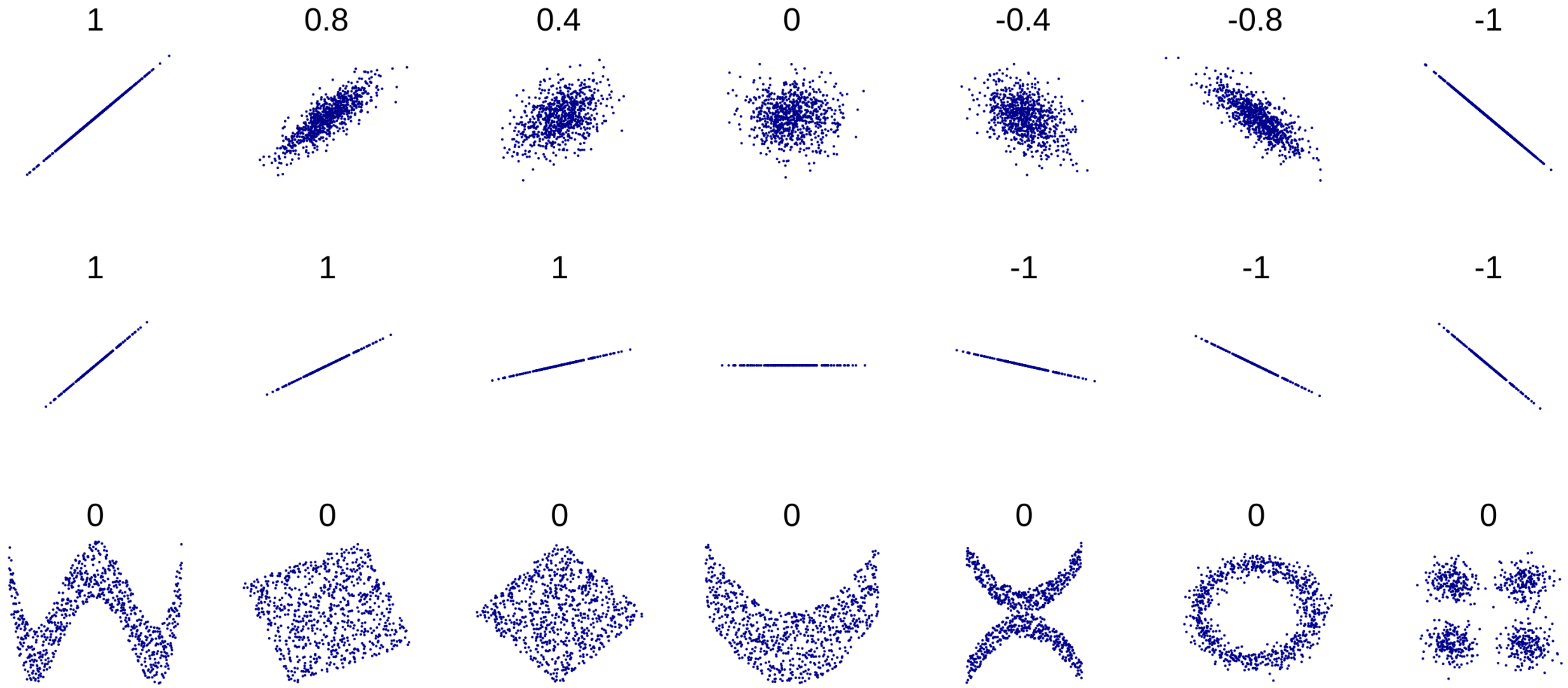
What media says

- Proving causality is hard and involves randomized controlled trials (or **causal inference**)
- Be cautious to conclude causality from correlations.

Anderson, S. E. (2016). *The Journal of pediatrics*
Media images from Internet

No correlation doesn't imply independence

Correlation only quantifies **linear** relationship



Correlation is not necessarily transitive

- ❑ X positively correlates with Z
- ❑ Z positively correlates with Y

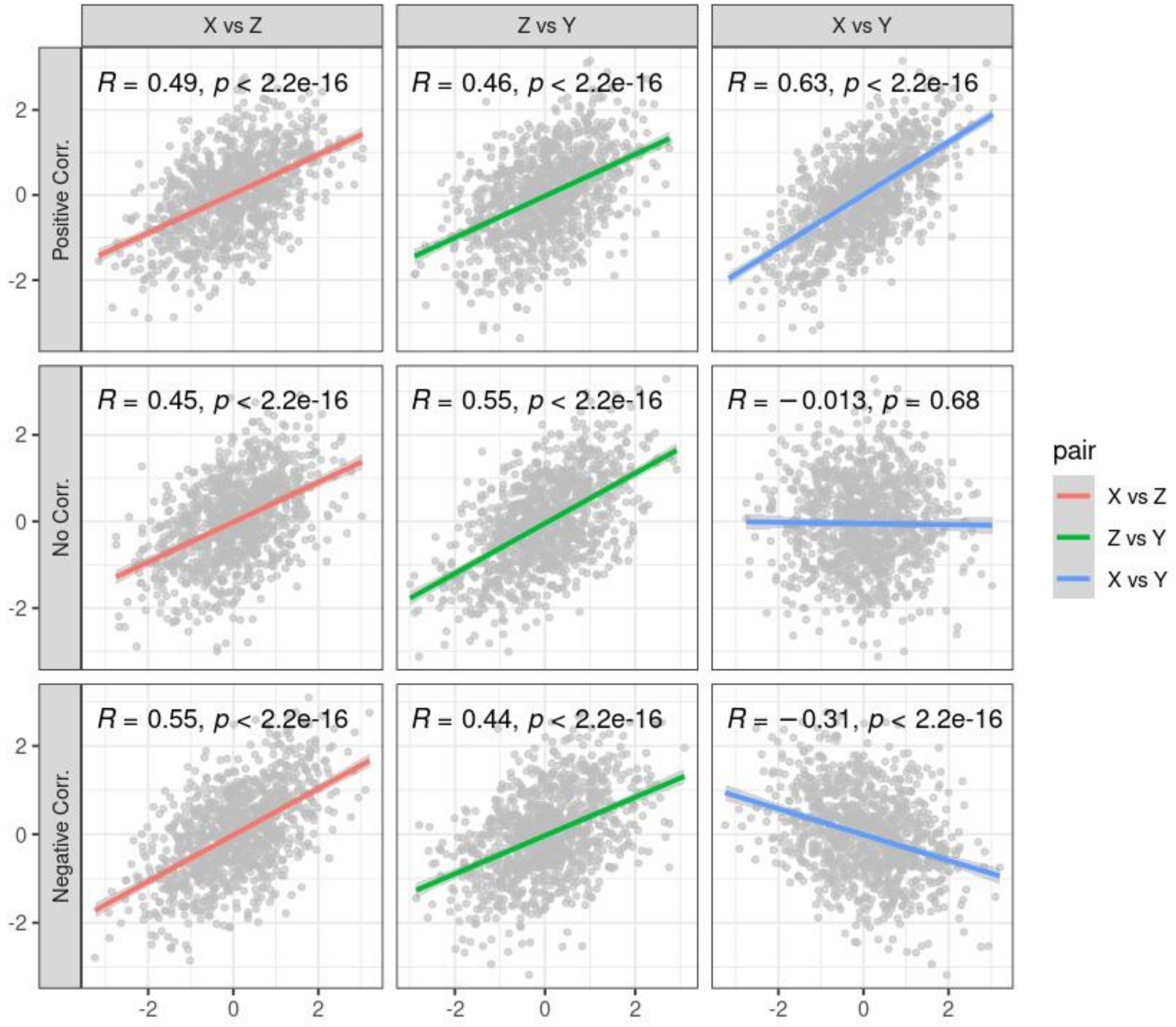
Question: How are X and Y correlated?

Well, everything is possible

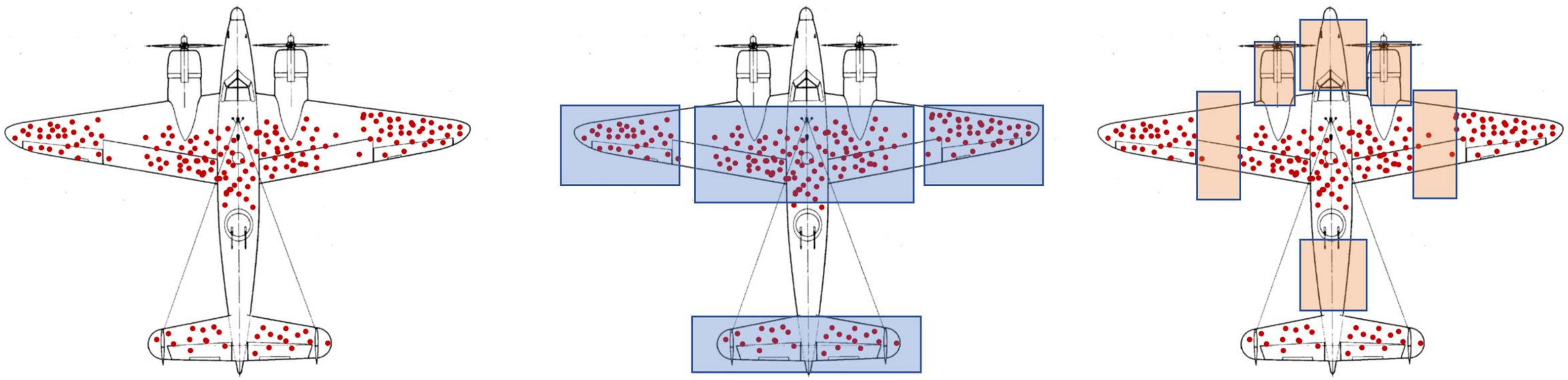
Simulation examples:

$$\begin{pmatrix} x \\ y \\ z \end{pmatrix} \sim N\left(\begin{bmatrix} 0 \\ 0 \\ 0 \end{bmatrix}, \begin{bmatrix} 1 & ? & 0.5 \\ ? & 1 & 0.5 \\ 0.5 & 0.5 & 1 \end{bmatrix}\right)$$

[When is correlation transitive?]



Survival (selection) bias



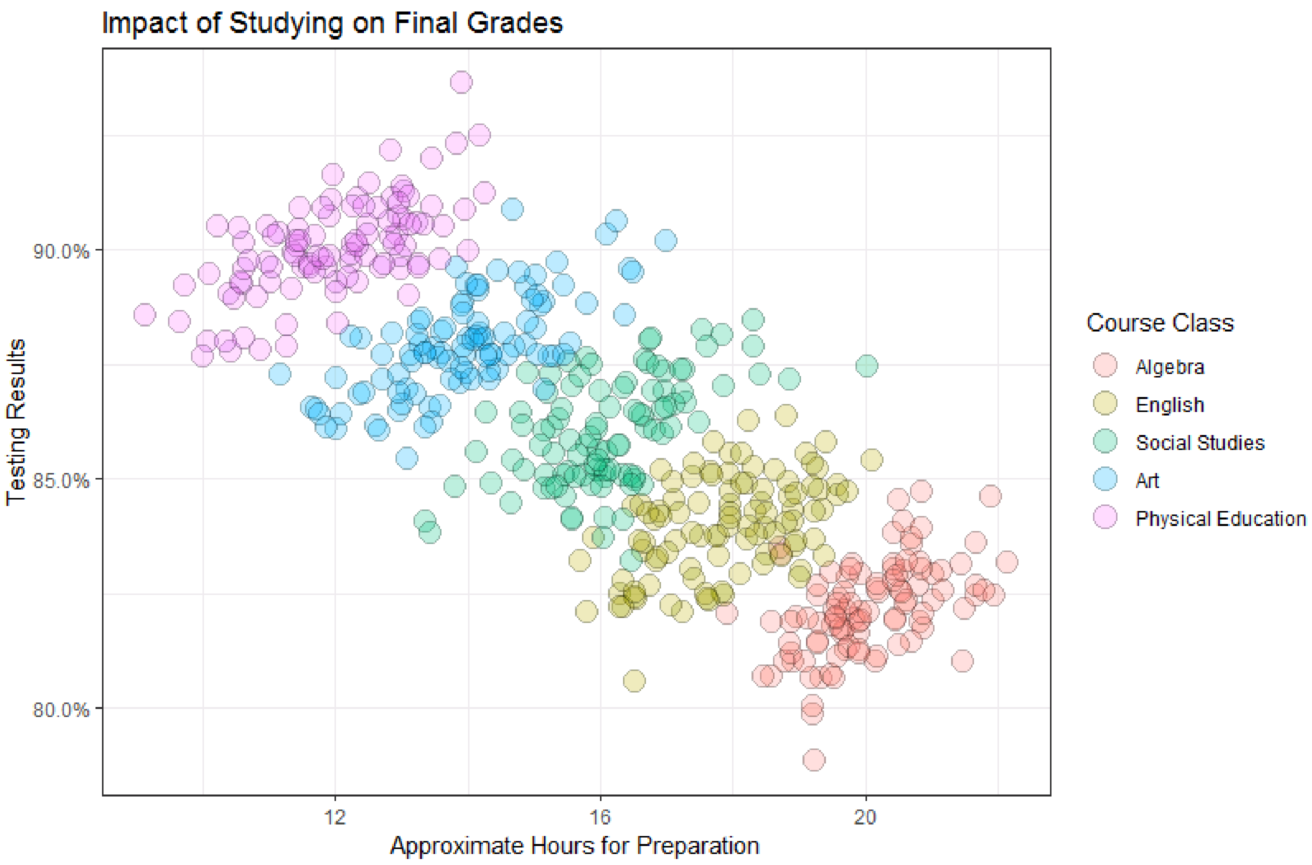
Our data if only from returning flights. Here we is a visualization of the places that bullet holes were observed.

And initial guess at how to fix this might be to apply additional armor platting to the parts of the plane with the most holes…

…. However this is where planes that *returned* had bullet holes. The planes we want to protect are the ones that did *not* return, so we should place armor there.

Simpson's paradox

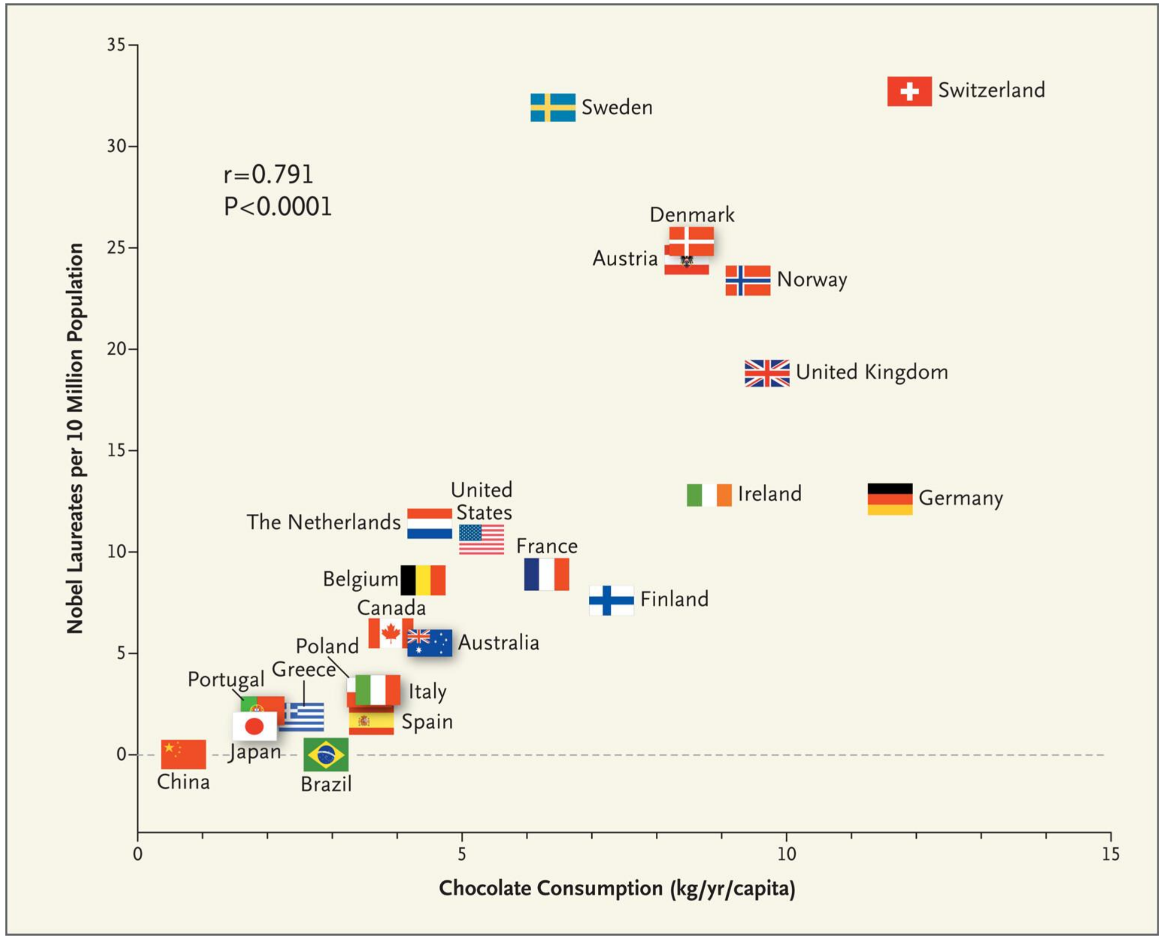
The trend reverses when groups of data are combined



Zoom-out errors

Ecological fallacy

Making false claims at individual level based on group averages



Zoom-in errors

Messerli, F. H. (2012). *N Engl J Med*

Thank you!

Q&A

Where to get help?

- https://chat.openai.com/
- https://stats.stackexchange.com/
- https://www.google.com
- https://www.3blue1brown.com
- https://statquest.org/

Valentine’s special!

Probability/distribution

Hypothesis testing

Model fitting