BMI/STAT-768

Statistical Methods for Medical Image Analysis

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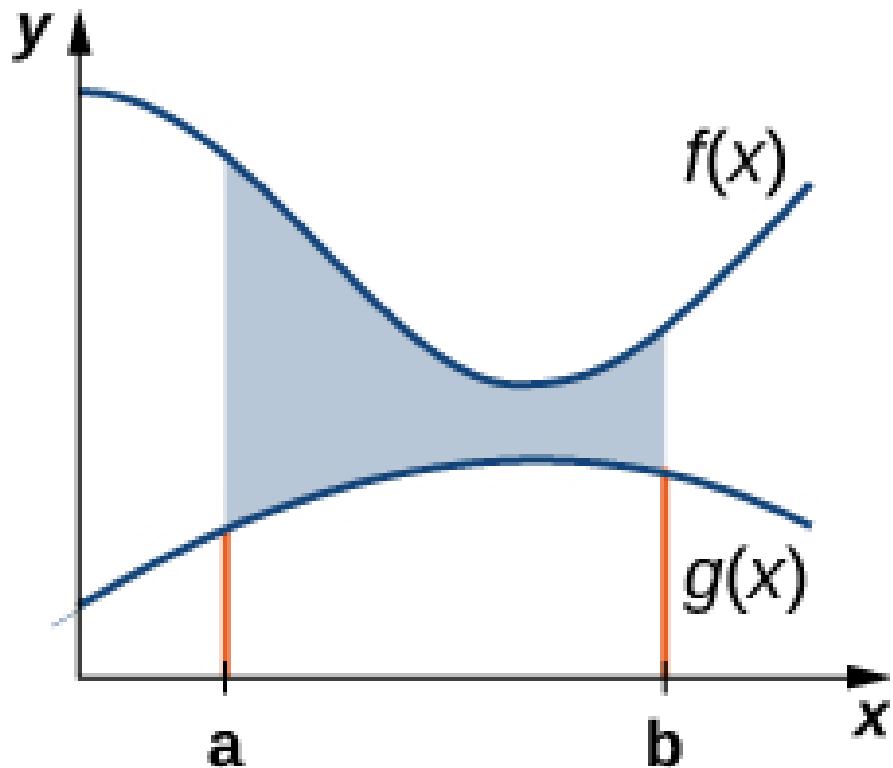
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Motivating problem

Test the equivalence of two functional data

Then compute *p*-value

A p-value is the probability, assuming the null hypothesis of no difference is true, of observing data at least as extreme as those actually observed.

How?

Permutation resampling

Path enumeration for exact probability computation

p-value computation in statistical inference

Data augmentation in deep learning

Unit Objectives

1) Understand the permutation group

2) Able to enumerate permutations

3) Able to generate permutations

4) Able to perform the permutation test – and obtain p-values

References

Hayasaka, S. Nichols, T.E. Validating cluster size inference: random field and permutation methods NeuroImage 20:2343-2356 http://www.sciencedirect.com/science/article/pii/S1053811903005020

Chung, M.K. et al. 2019. Rapid Acceleration of the permutation test via transpositions, *International Workshop on Connectomics in NeuroImaging*, Lecture Notes in Computer Science 11848:42-53.

Permutation Test

R.A. Fisher invented the method in 1935 in <u>The Design of Experiments</u>. This is the exact procedure for computing p-value.

Does not assume any statistical distribution- nonparametric.

Requires permutation invariance: exchangability under the equivalence of null hypothesis: two groups.

•There may be a situation we cannot permute.

Wide use of permutation test

Google scholar 888,000 papers.

One of the most widely used method in brain imaging. Why?
- **Exact and easy to understand. No need to study statistical models.**

Deep learning – Permutation invariant resampling: 14,000 deep papers related to permutations.

Permutation group

$$\mathbf{x} = (x_1, x_2, \cdots, x_m) \qquad \mathbf{y} = (y_1, y_2, \cdots, y_n)$$

$$(\mathbf{x}, \mathbf{y}) = (x_1, \cdots, x_m, y_1, \cdots, y_n)$$

$$\pi(\mathbf{x}, \mathbf{y}) \in \mathbb{S}_{m+n}$$ Permutation group of order *m+n*

$$(x_1, y_1, x_3, \cdots, x_m, x_2, y_2, \cdots, y_n)$$

Number of permutations $$\binom{m+n}{m} = \frac{(m+n)!}{m!n!}$$

`Permutability`

$$\mathbf{x} = (x_1, x_2, \cdots, x_m) \qquad \mathbf{y} = (y_1, y_2, \cdots, y_n)$$

$$(1, 3) = (2, 4)$$

Null hypothesis: $f(\mathbf{x}) = f(\mathbf{y})$ $\qquad 2 = 3$

$$(\mathbf{x}, \mathbf{y}) = (x_1, \cdots, x_m, y_1, \cdots, y_n)$$

$$\pi \quad (x_1, y_1, x_3, \cdots, x_m, x_2, y_2, \cdots, y_n)$$

Permutability: $f(\pi(\mathbf{x})) = f(\pi(\mathbf{y}))$

Number of permutations in permuting group labels

Number of permutations in literature

Fisher 1935, The Design of Experiment

$$\binom{8}{4} = 70$$

Thompson et al. 2001, Nature Neuroscience

$$\binom{40}{20} = 1.34 \cdot 10^{11}$$

Nichols et al. 2002, Human Brain Mapping
4279 citations

$$\binom{6}{3} = 20 \qquad AAAAAA|BBB$$

test

[Serious computational bottleneck](#) in brain imaging

1) Need to permute million voxels.
2) Compute the statistic for each permutation

Thompson et al. 2001 used <u>supercomputer</u>:
1million permutations from

$$\binom{40}{20} = 1.34 \cdot 10^{11} \quad \text{hundred billion permutations}$$

→ Transposition test (online test) bypass the bottleneck
Used masterfully by a previous student
http://arxiv.org/pdf/2012.00675.pdf
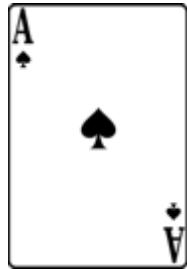
Hypothesis testing via permutat
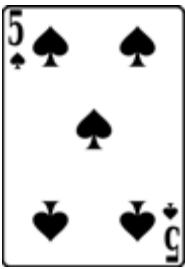
1. Set up reasonable null and and alternate <u>hypothesis</u>

2. Set up a function (<u>statistic</u>) that measures the strength of claims *against null*

3. Compute the <u>probability</u> about the statistic in the sample space generated by the permutation test

Sample space
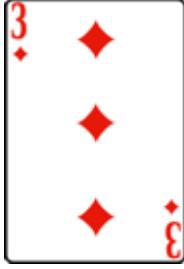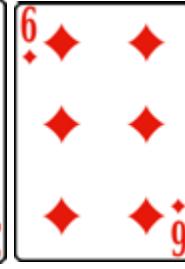
1   5   3   6
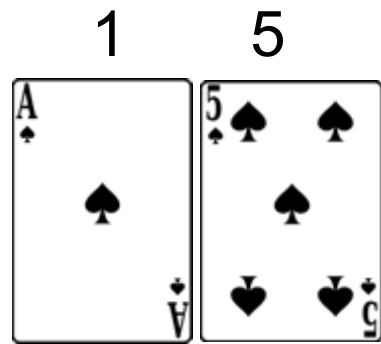
Player 1   Player 2   Observed data
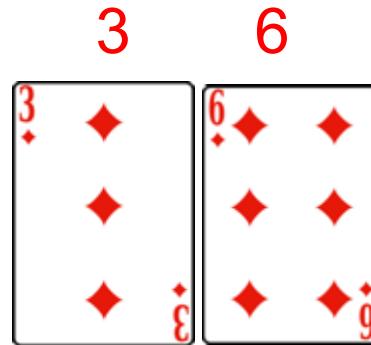
What is the likelihood (probability) of this event (observed data) happening?

$$\binom{4}{2} = 4 * 3/2 = 6$$

Sample space = all possible permu

| 1 | 5 |

Player 1

| 3 | 6 |

Player 2

Observed data

1	5		3	6
1	3		5	6
3	5		1	6
1	6		3	5
6	5		3	1
6	3		1	5
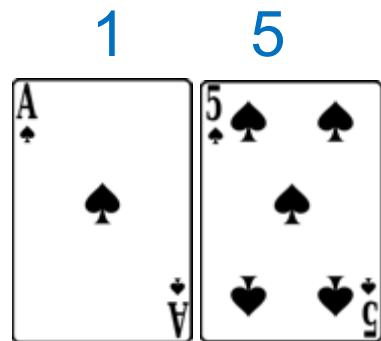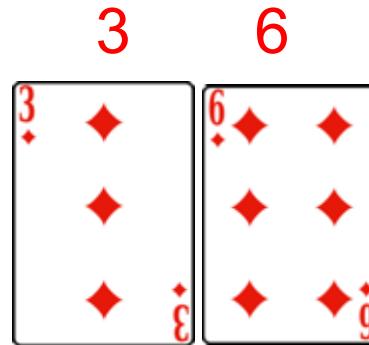
Generate the sample space using only observations

How to <u>design</u> a two-sample test?

1 5

3 6

Observed data

Player 1

Player 2

What is the likelihood (probability) of Player 1 and Player 2 have the same <u>card power</u>?

How to formulate the problem?

Denote X_j and Y_j as the values of cards for Player 1 and 2 respectively.

$$\sum_{j=1}^{m} X_j \qquad \sum_{j=1}^{m} Y_j$$

Power = sum of card values:

Test statistic – one sided

$$\sum_{j=1}^{m} X_j > \sum_{j=1}^{m} Y_j \qquad \rightarrow \quad \text{Player 1 has better cards}$$

Test statistic (distance): $\quad d = \sum_{j=1}^{m} X_j - \sum_{j=1}^{m} Y_j$

Observed
distance=-3   1   5   3   6

$$H_0 : d = 0 \qquad \rightarrow \quad \text{Player 1 and 2 have similar cards}$$

$$vs.$$

$$H_1 : d \geq 0 \qquad \rightarrow \quad \text{Player 1 has better cards}$$

$$H_1 : d \leq 0 \leftarrow Player\ 2\ has\ better\ cards$$

Distribution of test statistic

$$d = \sum_{j=1}^{m} X_j - \sum_{j=1}^{m} Y_j$$

1	5		3	6	Observation = -3
1	5		3	6	-3
1	3		5	6	-7
3	5		1	6	1
1	6		3	5	-1
6	5		3	1	7
6	3		1	5	3
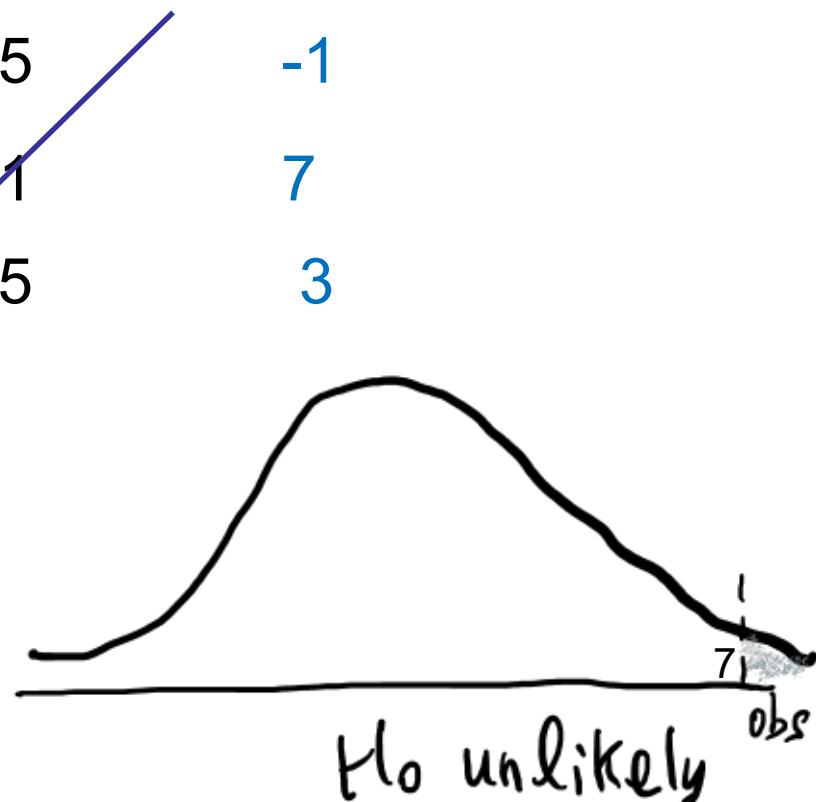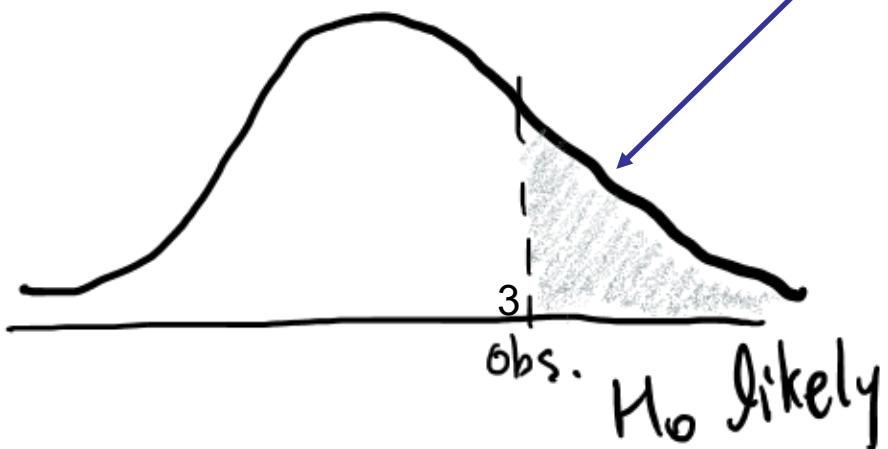
$$P(d \geq -3) = 4/6$$

3
obs. H_0 likely

7
H_0 unlikely   obs

$$H_0 : d = 0$$

$$vs.$$

$$H_1 : d > 0$$


obs. Ho likely

Ho unlikely obs
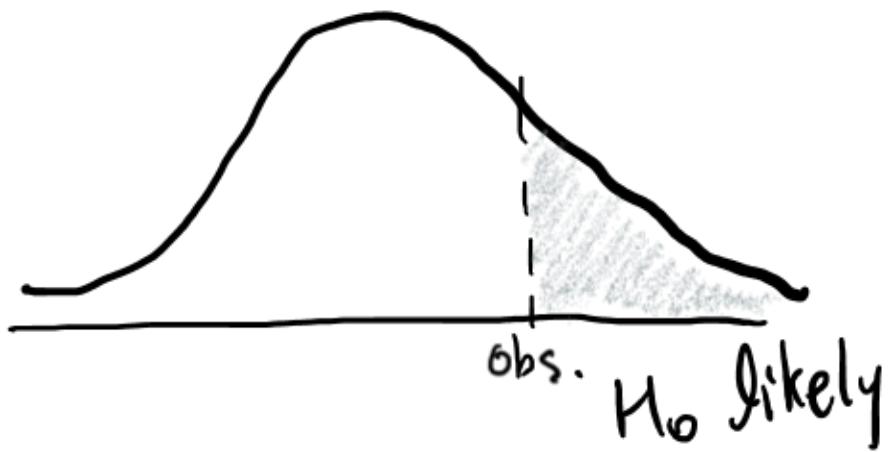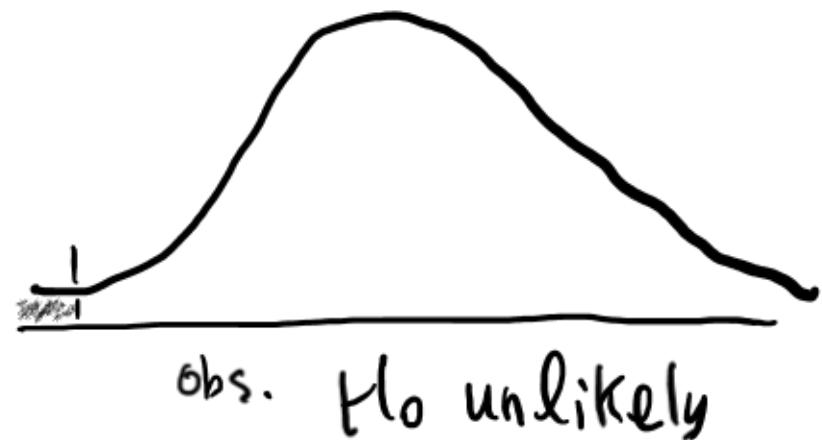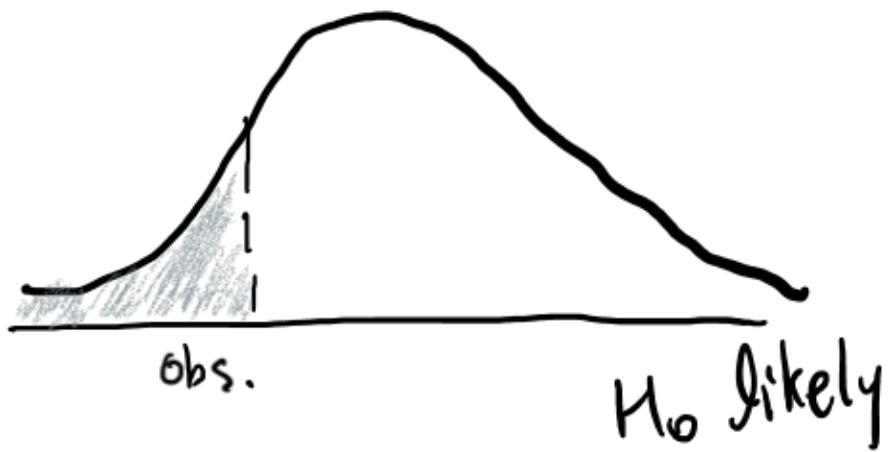
Definition: $pvalue = P(d \geq observation)$

Interpret *p*-values as continuous indices of the strength of claim (H_0) or alternate claim (H_1)

$$H_0 : d = 0$$

$$vs.$$

$$H_1 : d < 0$$

obs. H_0 likely   obs. H_0 unlikely
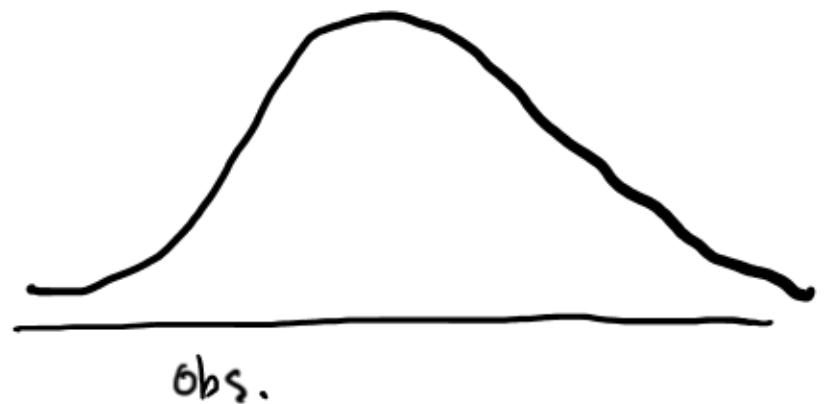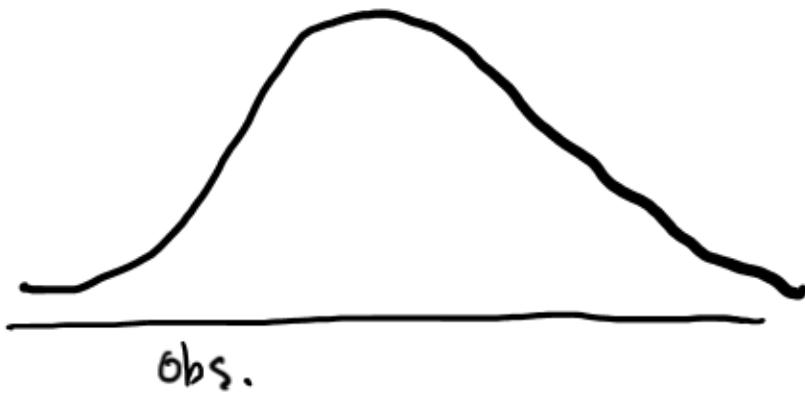
Definition: $pvalue = P(d \leq observation)$

Test statistic – two sided

$H_0 : d = 0$

$vs.$

$H_1 : d \neq 0$

$$P(|d - observation| > \epsilon)$$

$$pvalue = P(d \leq -|observation|) + P(d \geq |observation|)$$

p-value in the permutation test

$$\mathbf{x} = (x_1, x_2, \cdots, x_m) \qquad \mathbf{y} = (y_1, y_2, \cdots, y_n)$$

$$(\mathbf{x}, \mathbf{y}) = (x_1, \cdots, x_m, y_1, \cdots, y_n)$$

$$\pi(\mathbf{x}, \mathbf{y}) \in \mathbb{S}_{m+n}$$

observation
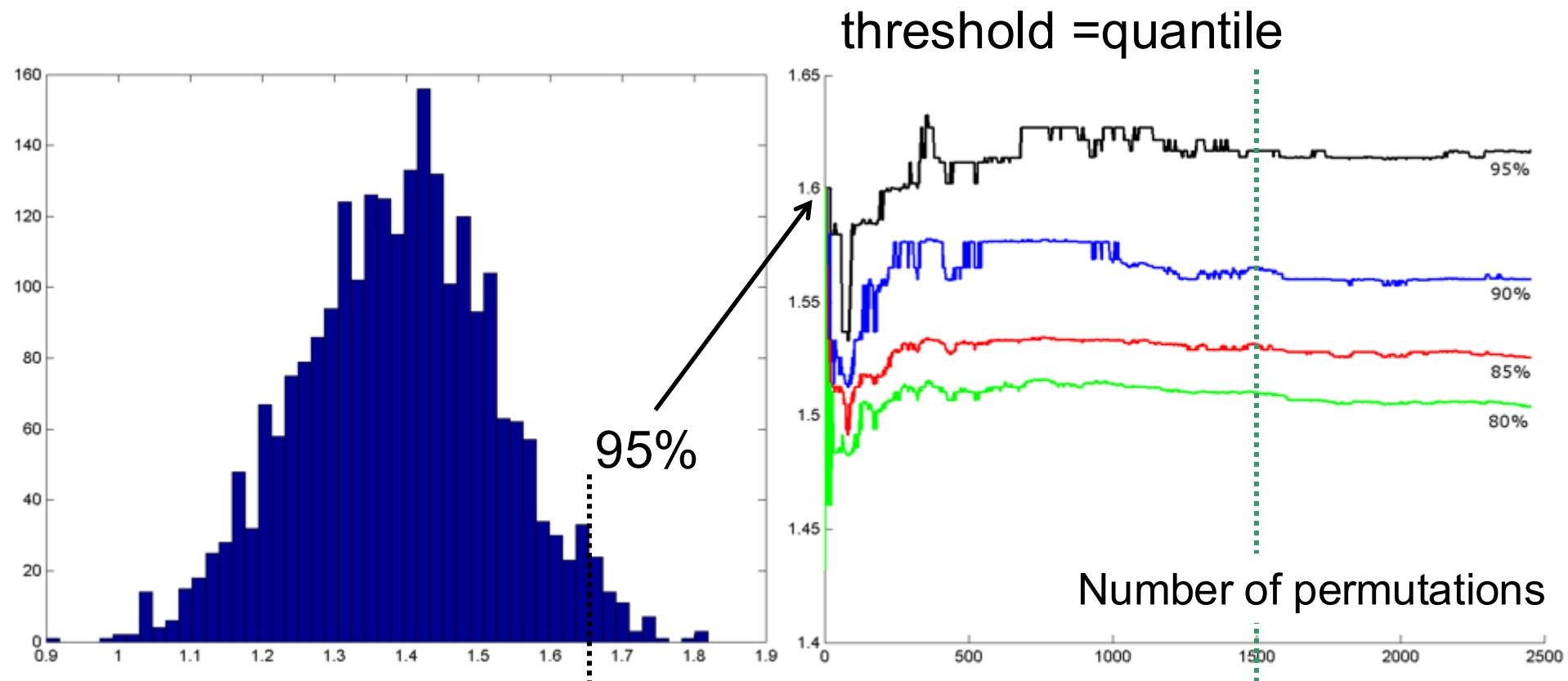
$$p\text{-value} = \frac{1}{(m+n)!} \sum_{\pi \in \mathbb{S}_{m+n}} \mathcal{I}\Big(f(\mathbf{x}, \mathbf{y}) \leq f(\pi(\mathbf{x}), \pi(\mathbf{y}))\Big)$$

If you work out symmetry, you can reduce this to m+n choose m
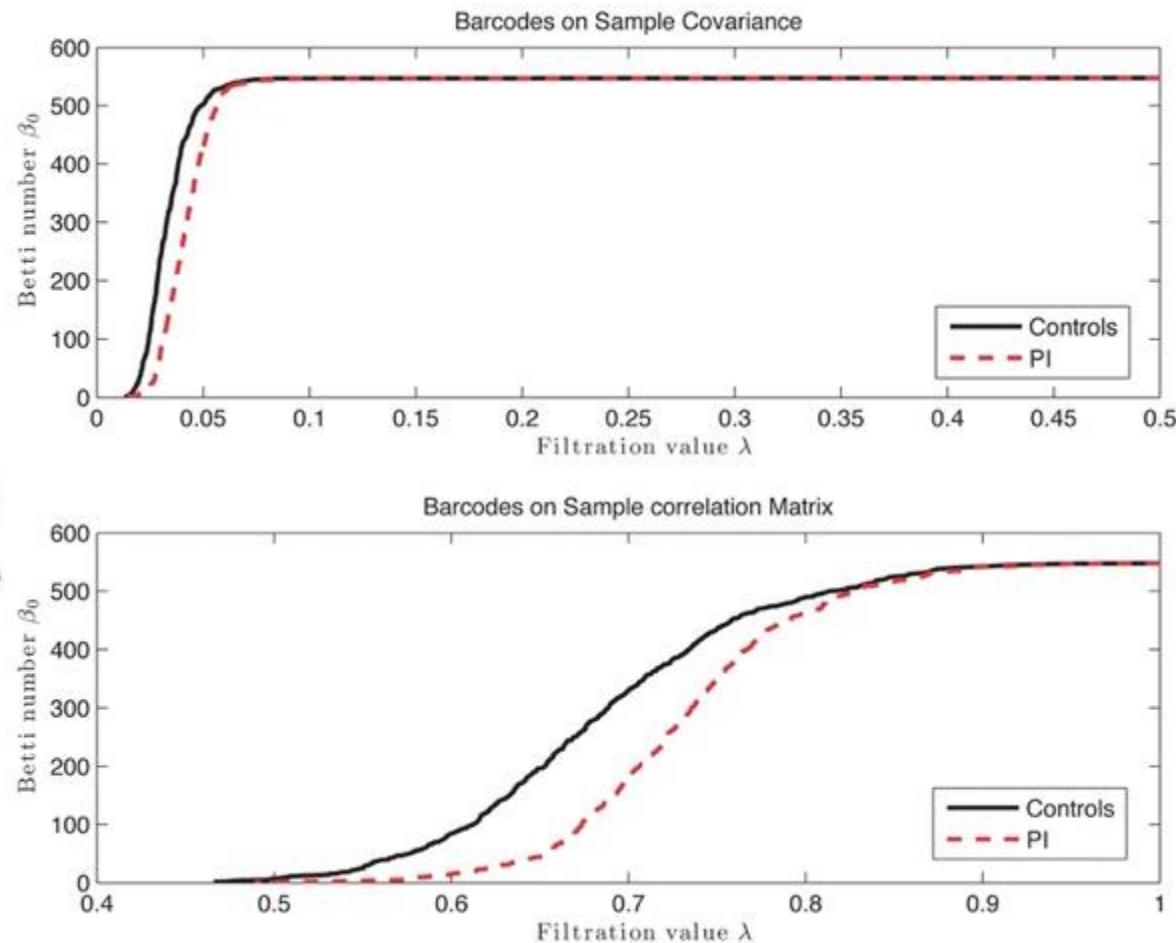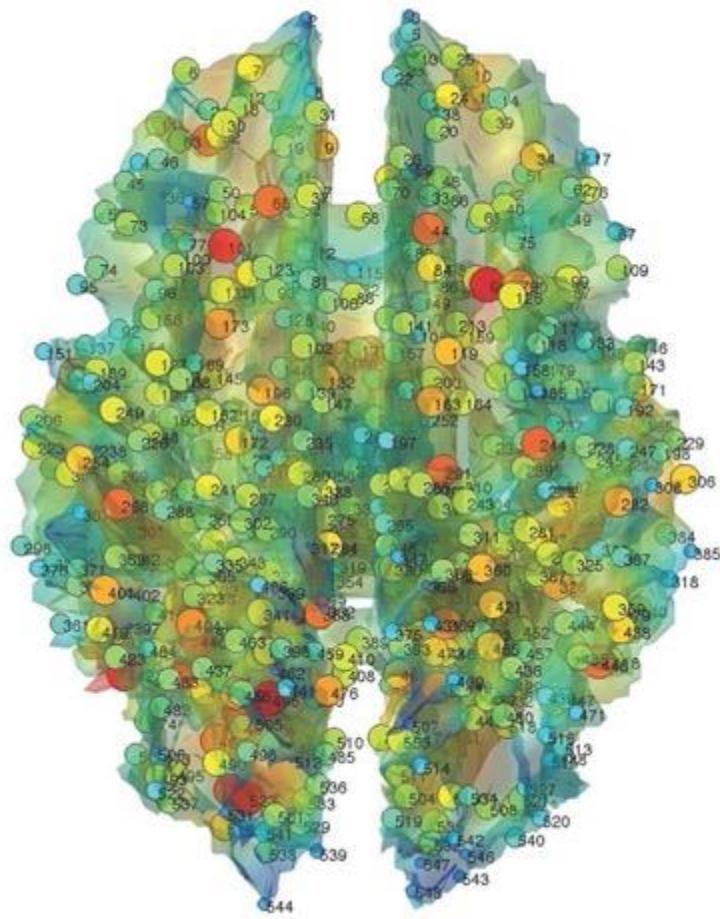
Test statistic over permutations

Exercise. Set up an iterative computational procedure

How to numerically check the convergence of permutation test

threshold =quantile

95%

95%

90%

85%

80%

Number of permutations

Example: permutation test on 1D functional data: barcodes in TDA or cumulative distribution functions (CDF)

Average barcodes

Chung et al. 2015 TMI
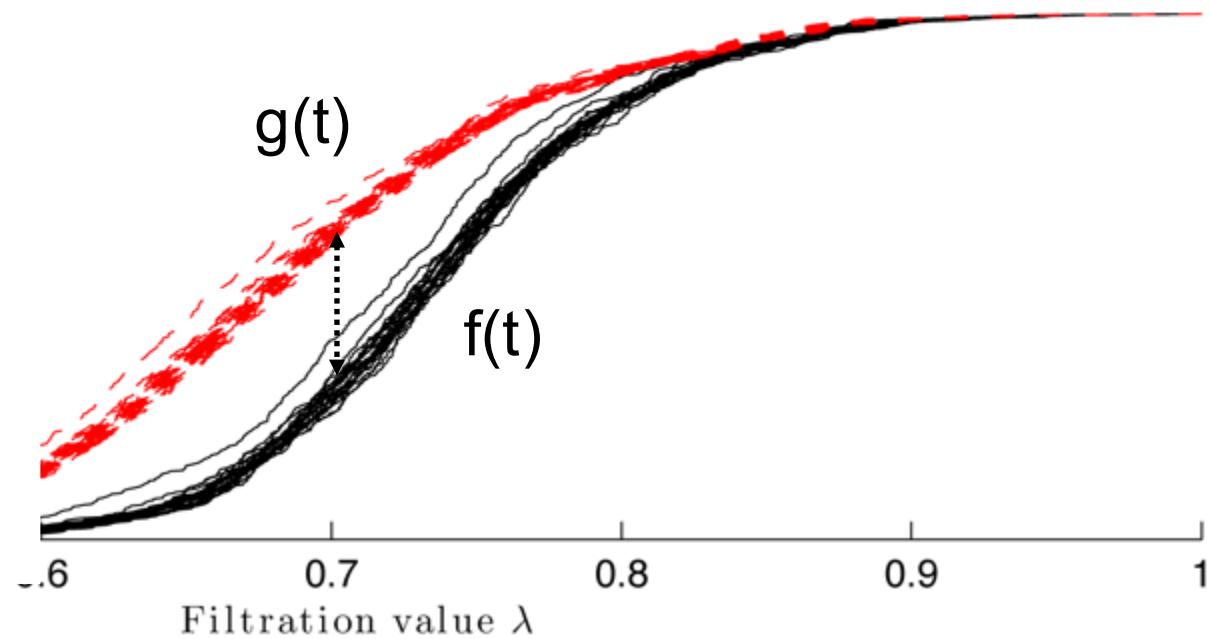
# Barcodes for all the subjects

$$d(f_i, g_j) = \sup_t |f_i(t) - g_j(t)|$$

s on Jacknife Resampling on Sparse Correlation

g(t)

f(t)

.6   0.7   0.8   0.9   1

Filtration value λ
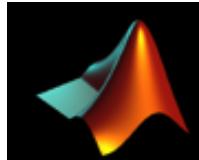
Test statistic
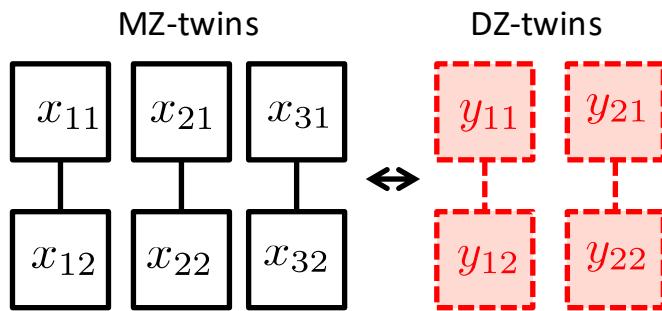
$$\sup_t |\bar{f}(t) - \bar{g}(t)|$$

Matlab
demo

Permutation test on a collection of barcodes and determine the statistical significance of curve shape differences.
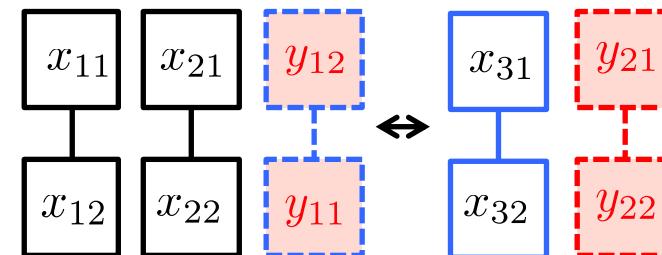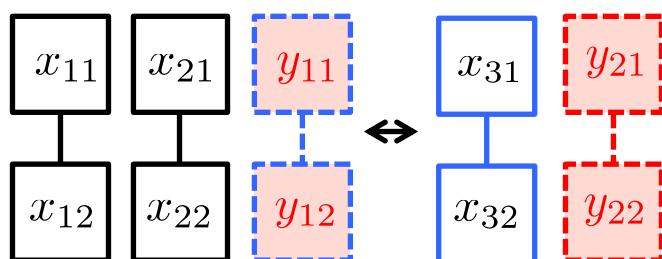
Example: Permutation of paired data –twins

MZ-twins

DZ-twins
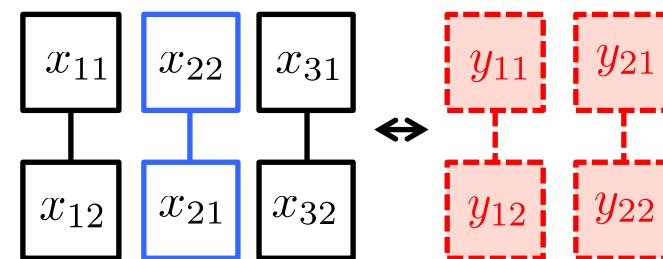
Permutation is the composition of two types of permutations

Permutation between groups

Permutation within twins

Used masterfully by a previous student in
Annals of Applied Statistics 2023 http://arxiv.org/pdf/2012.00675.pdf

Permutation of paired data

The sample space is generated by the permutation within and between groups.
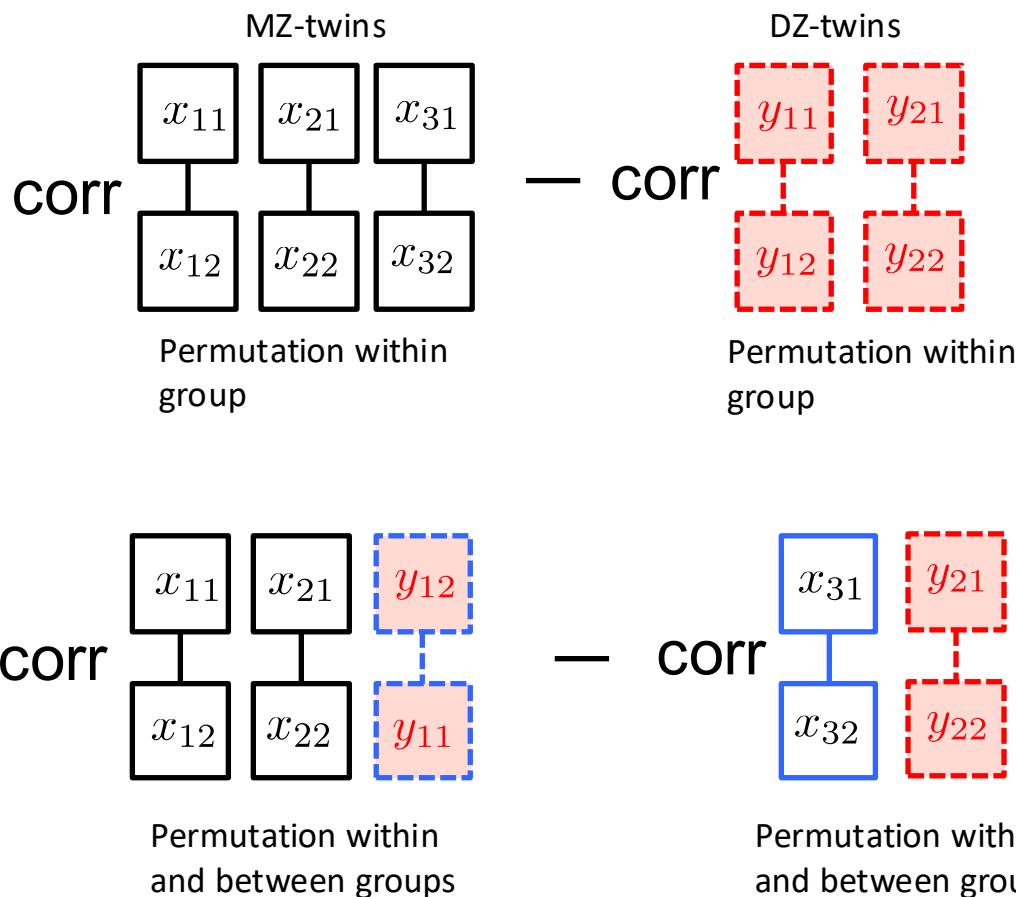
$$\text{\# of permutations} = 2^{m+n-2} \binom{m+n}{n}$$

Exercise. Determine if it is the correct number of permutations.

The sample space is so large, you need extremely fast algorithm
→ online algorithms for resampling -transpositions

Permutation of paired data

MZ-twins   DZ-twins

corr
$\boxed{x_{11}}\ \boxed{x_{21}}\ \boxed{x_{31}}$
$\boxed{x_{12}}\ \boxed{x_{22}}\ \boxed{x_{32}}$

$-\ \text{corr}$
$\boxed{y_{11}}\ \boxed{y_{21}}$
$\boxed{y_{12}}\ \boxed{y_{22}}$

Observed test statistic

Permutation within group

Permutation within group

corr
$\boxed{x_{11}}\ \boxed{x_{21}}\ \boxed{y_{12}}$
$\boxed{x_{12}}\ \boxed{x_{22}}\ \boxed{y_{11}}$

$-\ \text{corr}$
$\boxed{x_{31}}\ \boxed{y_{21}}$
$\boxed{x_{32}}\ \boxed{y_{22}}$

test statistic under the permutation within and between groups

Permutation within and between groups

Permutation within and between groups

PROJECT 18 Structure-Preserving Permutation Tests for Directed Time-Series Data

Goal: Develop a statistically principled permutation framework for testing directed dependence in time-series data, such as time-lagged correlations or transfer entropy, that preserves intrinsic temporal structure while destroying directed causal effects under the null hypothesis of no directional influence.

Discerption: This project aims to design a valid permutation test for directed statistics such as lagged correlation, Granger causality, or transfer entropy. Let X_t and Y_t be two time series and let $T(X \rightarrow Y)$ denote a directional measure. The null hypothesis is H_0: no directed influence from X to Y. Standard random shuffling breaks temporal dependence and invalidates inference. The goal is to construct permutation schemes that preserve autocorrelation and marginal structure of each series while destroying cross-lag dependence $X_{t-l} \rightarrow Y_t$.

We solve the problem in the spectral domain by representing directed interactions as edge flows and performing a 1-Hodge decomposition on the directed network constructed from lagged interactions. By selectively permuting the components corresponding to the gradient (non-cyclic) or harmonic (cyclic) components, we construct a structure-preserving (topology-preserving) null model. If we permute the gradient component, we disrupt acyclic directional structure while preserving cyclic structure. If we permute the harmonic component, we disrupt global cyclic structure while preserving local acyclic structure and the underlying topology. Investigate these two topology preserving permutation methods.

Learning Outcomes: Students will understand how directed dependence in time series is defined through lagged relationships and how measures such as Granger causality and transfer entropy quantify directional influence. They will learn why standard permutation methods fail for temporally dependent data and how to design structure-preserving null models that underlying structure.

Students will gain experience implementing topology-aware permutation tests based on Hodge theory, aligning permutation strategies with specific hypotheses about acyclic or cyclic structure. By the end of the project, they will be able to develop, justify, and evaluate statistically valid inference procedures for directed network data.

Have you ever seen the permutation test on three groups?

$$\mathbf{x} = (x_1, x_2, \cdots, x_m)$$

$$\mathbf{y} = (y_1, y_2, \cdots, y_n)$$

$$\mathbf{z} = (z_1, z_2, \cdots, z_l)$$

Why there is no 3-sample or 4-sample permutation test?

Other Resampling Techniques

Permutation test
   Resampling in two samples

Jackknife
   Resampling without replacement

Bootstrap
   Resampling with replacement

History: Jackknife

Mosteller and Tukey (1977, p. 133) described a resampling method, the jackknife, in the following way:

"The name 'jackknife' is intended to suggest the broad usefulness of a technique as a substitute for specialized tools that may not be available, just as the Boy Scout's trustworthy tool serves so variedly..."

Resampling without replacement

1   2   3   4

leave-one-out
(2 3 4), (1 3 4), (1 2 4), (1 2 3)

leave-two-out
(3 4), (2 4), (2 3), (1 4), (1 3), (1 2)

For sample size n, leave-k-out
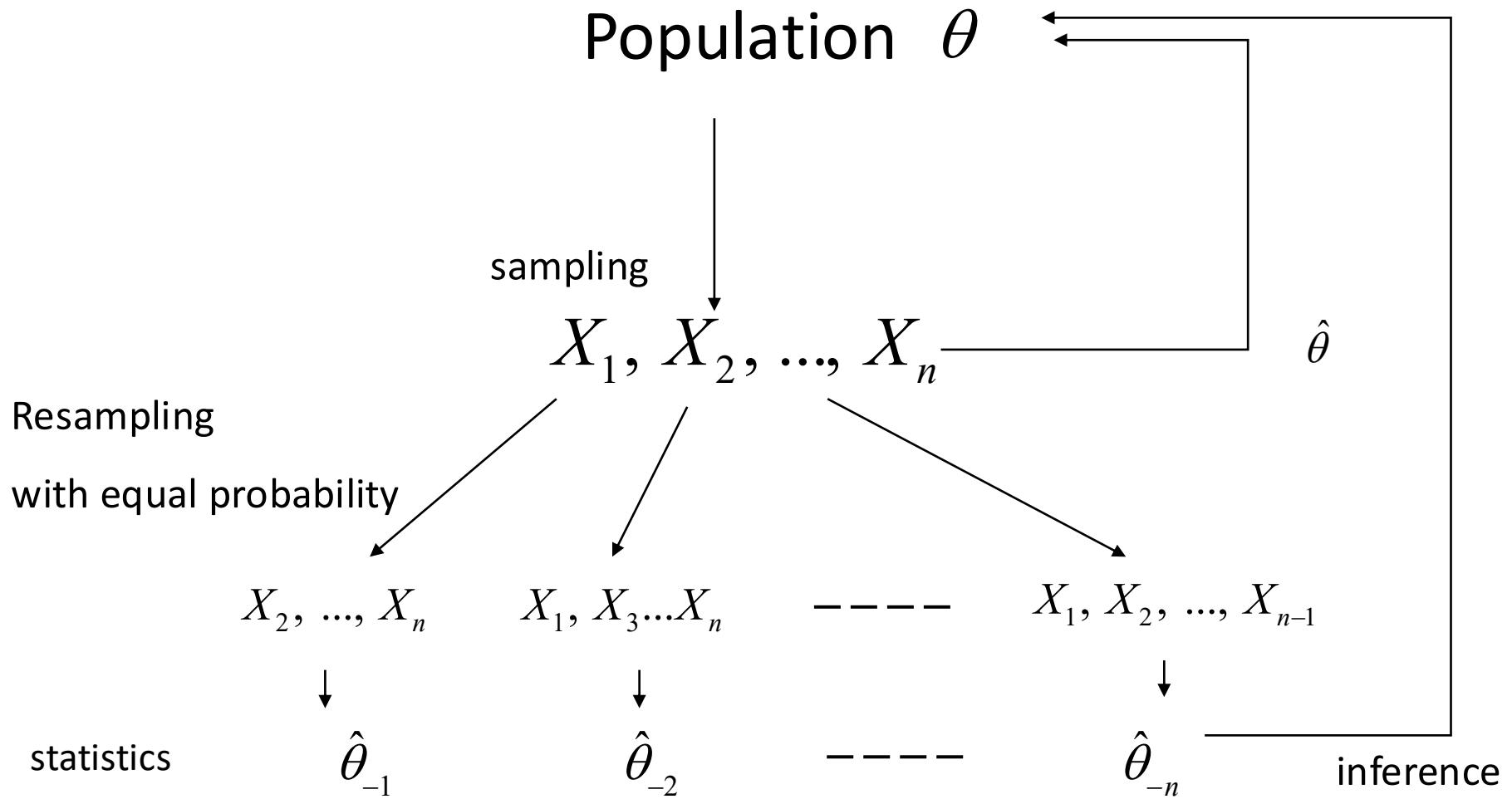
$$\left(\begin{array}{c} n \\ k \end{array} \right) = \frac{n!}{(n-k)!k!}$$

Jackknife resampling method

For a group with n subjects, one subject is removed and the remaining n-1 subjects are used in computing statistics (leave-one-out scheme).

This process is repeated for each subject to produce n statistics.

Schematic of Jackknife

Population θ

sampling

$X_1, X_2, ..., X_n$ $\quad\hat{\theta}$

Resampling

with equal probability

$X_2, ..., X_n$ $\qquad$ $X_1, X_3...X_n$ $\qquad$ $----$ $\qquad$ $X_1, X_2, ..., X_{n-1}$

$\downarrow$ $\qquad\qquad\qquad$ $\downarrow$ $\qquad\qquad\qquad$ $----$ $\qquad\qquad$ $\downarrow$

statistics $\qquad$ $\hat{\theta}_{-1}$ $\qquad\qquad$ $\hat{\theta}_{-2}$ $\qquad\qquad$ $----$ $\qquad\qquad$ $\hat{\theta}_{-n}$ $\qquad$ inference

Jackknife

$$X_1, \ ..., \ X_n \overset{iid}{\sim} F(X; \theta)$$

population mean

$$X_1, \ X_2 ..., \ X_n \quad \mapsto \quad \hat{\theta}_{-1} = \frac{X_2 + ... + X_n}{n-1}$$

$$X_1, \ X_2 ..., \ X_n \quad \mapsto \quad \hat{\theta}_{-2} = \frac{X_1 + X_3 + ... + X_n}{n-1}$$

$$\vdots \qquad\qquad\qquad \vdots$$

$$X_1, \ X_2 ..., \ X_n \quad \mapsto \quad \hat{\theta}_{-n} = \frac{X_1 + ... + X_{n-1}}{n-1}$$

Jackknife estimation

Leave-one-out mean

$$\mu_{(i)} = \frac{1}{n-1}\sum_{j\neq i} X_j = \frac{n\bar{X} - X_i}{n-1}$$

Jackknife estimate of mean

$$\mu_{(.)} = \frac{1}{n}\sum_{i=1}^{n} \mu_{(i)} = \frac{n}{n-1}\bar{X} - \frac{1}{n-1}\bar{X} = \bar{X}$$

Jackknife estimate of mean is unbiased.

Example: Correlation between gill weight and body weight in 12 crabs

Sample correlation
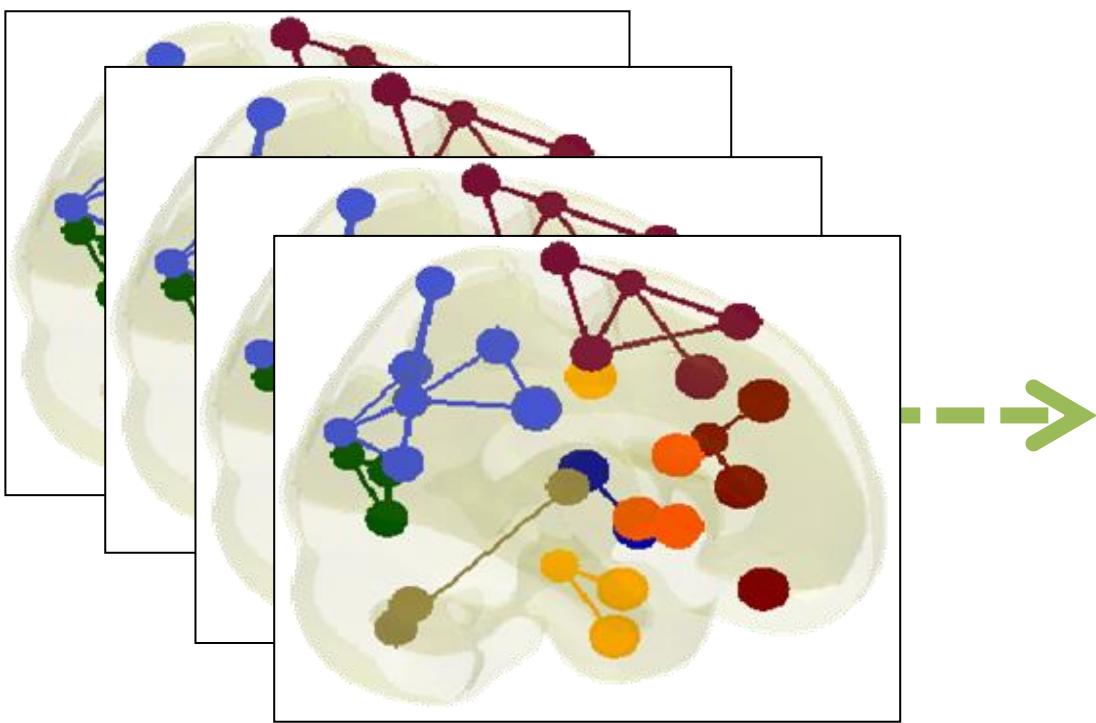
$r = 0.865$

Jackknife
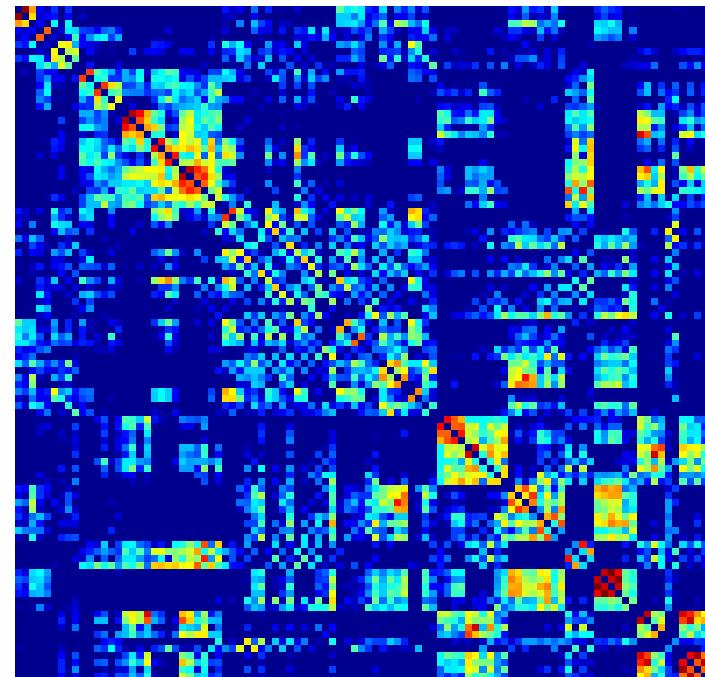
$r = 0.878$

Gill(mg)	Body(g)	r_{-i}	φ_i
1590	14.40	0.888	0.607
1790	15.20	0.884	0.656
10	11.30	0.892	0.570
450	2.50	0.830	1.249
3840	22.70	0.811	1.452
23	14.90	0.863	0.879
10	1.41	0.875	0.751
32	15.81	0.872	0.779
8	4.19	0.845	1.078
22	15.39	0.867	0.843
32	17.25	0.858	0.940
21	9.52	0.877	0.725

Example: Jackknife on correlation matrix

Multiple PET images on 90 voxels

90 x 90 correlation map per group

Lee, H. et al. 2012 IEEE Trans. Medical Imaging 31:2267-2277

MATLAB function

`y = randsample(n,k)` returns a k-by-1 vector y of values sampled uniformly at random, without replacement, from the integers 1 to n.

`jackstat = jackknife(jackfun,X)` draws jackknife data samples from the n-by-p data array X, computes statistics on each sample using the function jackfun, and returns the results in the matrix jackstat. jackknife regards each row of X as one data sample, so there are n data samples.

Cross-validation

Cross-validation is a model validation technique for estimating the performance of a (predictive) model.

Invented by statistician A.K. Kurtz in 1948
(A research test of Rorchach test, Personal Psychology 1:41-53). Extended further by Mosier (1951) and Krus and Fuller (1982)

3-fold cross-validation: splitting strategy

Dataset
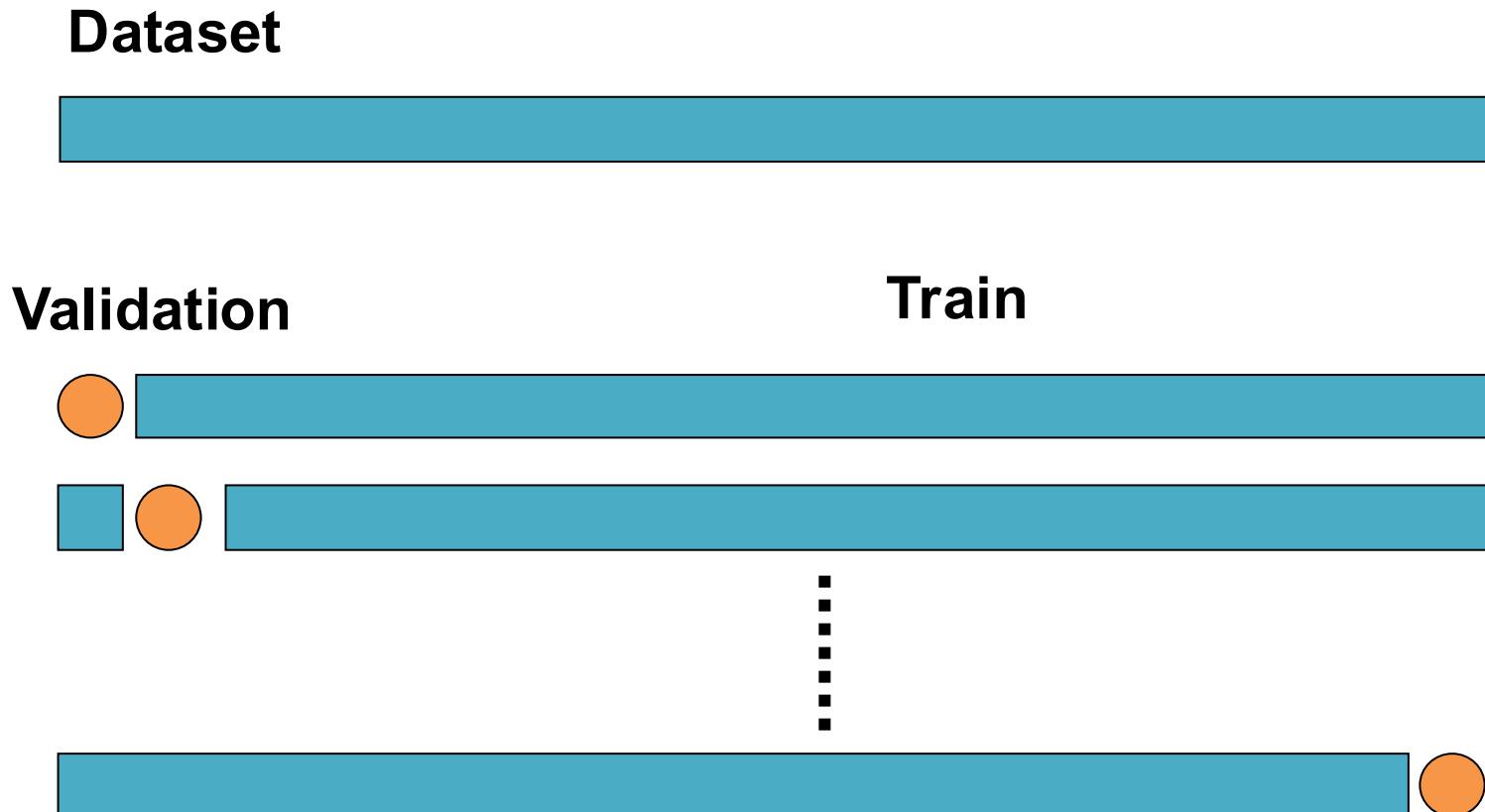
Training

Validation
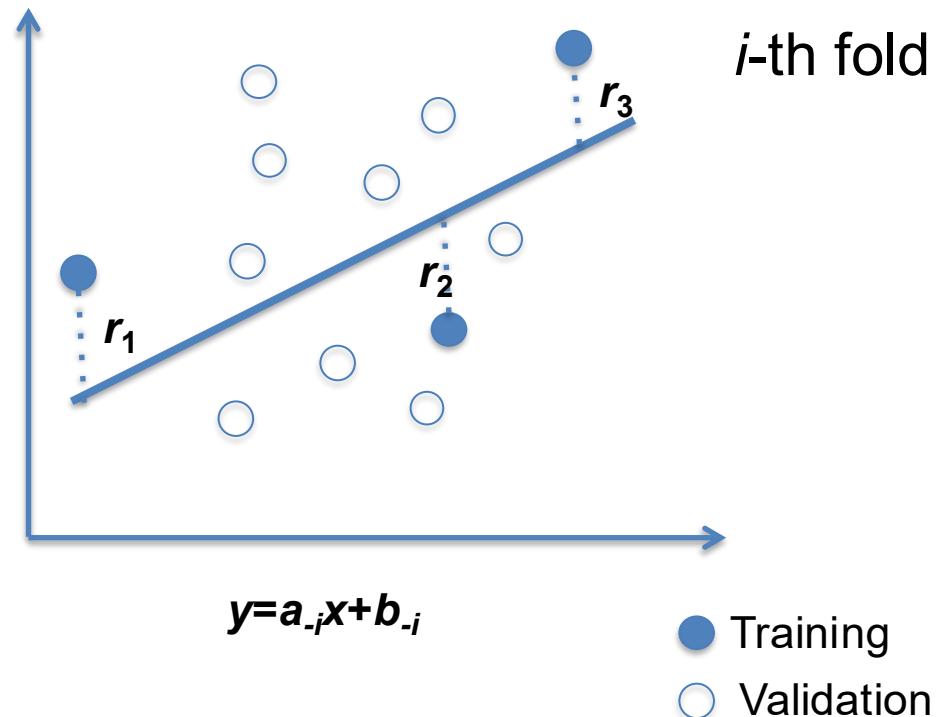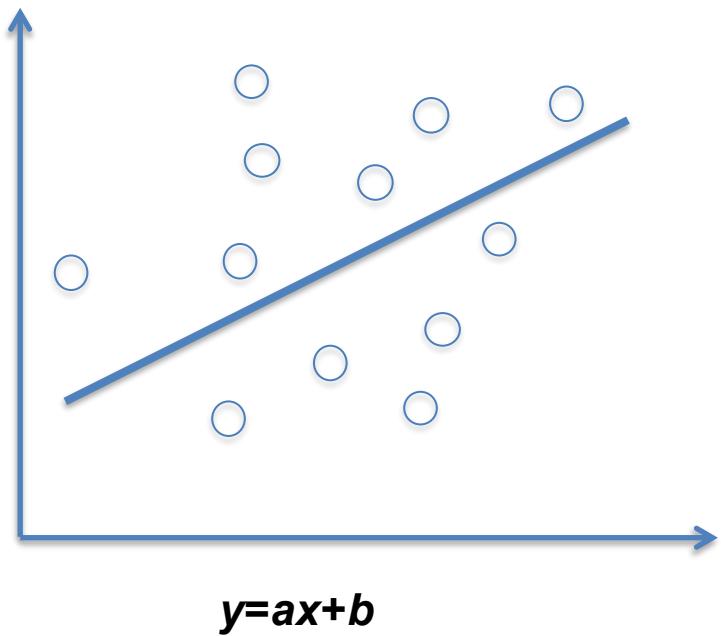
Leave-one-out cross-validation

Dataset

Validation   **Train**

Question: what is the optimal strategy for split?
Survey cross-validation strategy → project

Model Accuracy with k-fold cross-validation

$y=ax+b$

$y=a_{-i}x+b_{-i}$

i-th fold

● Training
○ Validation

Prediction error: the model accuracy is often measured in terms of the <u>sum of squared residuals</u>.

Bootstrap

In 1979, the statistician Brad Efron made an ingenious suggestion.

Most of what we know about the true probability distribution comes from the data. So let's treat the data as a *proxy* for the true distribution.

We draw multiple samples from this proxy. This is called *resampling*. And compute the statistic of interest on each of the resulting pseudo-datasets.

The start of modern statistics computation vs. theory

"Bootstrapping has requires very little in the way of modeling, assumptions, or analysis, and can be applied in an automatic way to any situation, no matter how complicated". *Efron and Gong 1983*

In *'Singular Travels, Campaigns and Adventures of Baron Munchausen'* by R. E. Raspe (1786), the main character, finding himself in a deep hole, extracts himself using only the straps of his boots.

Pull yourself by pulling the bootstrap

What is Bootstrapping?

BOOTSTRAP

Bootstrap resampling

- Introduced by Efron in 1979.

- Motivated by Jackknife.

- A "bootstrap" data set is one created by randomly selecting n points from the training set D, with replacement.

- In bootstrap estimation, this selection process is independently repeated B times to yield B bootstrap data sets.

Resampling with replacement

1   2 3 4

(1 1 1 1), (1 1 1 2), (1 1 1 3), ….., (4 4 4 3), (4 4 4 4)

(1 2 2 4) = (4 2 2 1)

$$\binom{2n-1}{n} = \frac{(2n-1)!}{n!(n-1)!}$$ possible resamples

Can be exhaustively large → Monte Carlo simulation

Problem: Prove the above combinations.

Proof: Resampling with replacement

1 2 3 4

(y_1, y_2, y_3, y_4)

$(1\ 1\ 1\ 1) \rightarrow (4, 0, 0, 0)$
$(1\ 2\ 2\ 4) \rightarrow (1, 2, 0, 1)$
$(4\ 2\ 2\ 1) \rightarrow (1, 2, 0, 1)$

Equivalent representation

Method 1) The number of nonnegative solutions in $y_1+y_2,+y_3+y_4 = 4$

# of grid points on the hyperplane.

Method 2) Replace # with bar and , with +:

| | | | + + +

| + | | + + |

| + | | + + |
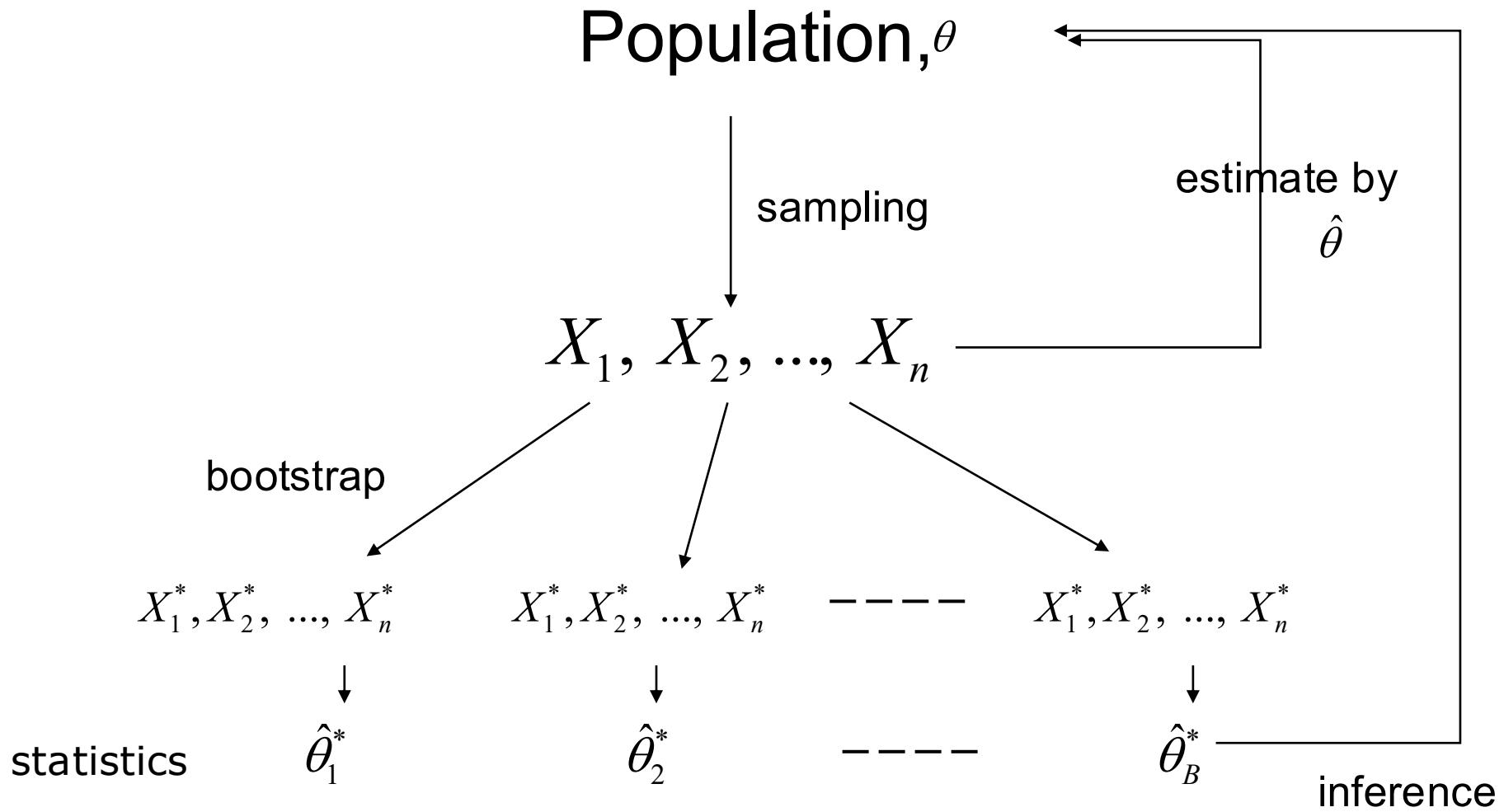
4 vertical lines + 3 plus signs

$$\begin{pmatrix} 4+3 \\ 4 \end{pmatrix}$$

possible solutions

The Bootstrap

- Data **D** = X_1, X_2, X_3, …. ,X_n $\rightarrow$ statistic s

- Bootstrap replicate:
    - **D***1 = X^*_1, X^*_2, X^*_3, …. ,X^*_n $\rightarrow$ statistic s*1
    - **D***2 = X^*_1, X^*_2, X^*_3, …. ,X^*_n $\rightarrow$ statistic s*2
    - …

- X^*_1, X^*_2, X^*_3, …. ,X^*_n are randomly selected with replacement, from X_1, X_2, X_3, …. ,X_n

- Usually use 1000-10,000 bootstrap replicates and obtain the empirical distribution

Schematic of Bootstrap

Population,θ

sampling

estimate by
$\hat{\theta}$

$$X_1, X_2, ..., X_n$$

bootstrap

$$X_1^*, X_2^*, ..., X_n^* \qquad X_1^*, X_2^*, ..., X_n^* \qquad ---- \qquad X_1^*, X_2^*, ..., X_n^*$$

$$\downarrow \qquad\qquad\qquad \downarrow \qquad\qquad\qquad\qquad\qquad \downarrow$$

statistics $\qquad \hat{\theta}_1^* \qquad\qquad\qquad \hat{\theta}_2^* \qquad\qquad ---- \qquad\qquad \hat{\theta}_B^*$

inference

Example: *Median Gill Weight in Crabs*

Gill weights (in mg):

159 179 100   45 384 230 100 320   80 220 320 210

Median = 195mg

													Median
Real	159	179	100	45	384	230	100	320	80	220	320	210	**195**

Bootstrap replicates:

B1	320	159	45	320	100	320	100	320	100	230	100	210	**185**
B2	384	384	45	384	45	384	100	80	45	179	230	230	**205**
B3	159	320	80	45	45	80	220	210	230	320	230	220	**215**
B4	220	179	384	100	80	100	230	230	179	230	384	45	**200**
B5	320	220	210	100	159	320	220	210	100	80	100	210	**210**
B6	80	100	230	100	210	384	159	220	320	45	45	210	**185**
B7	179	210	80	320	100	230	159	320	100	45	384	320	**195**
B8	384	159	100	159	100	179	100	179	220	384	220	159	**169**
B9	320	210	45	320	179	159	100	210	159	45	210	100	**169**

. . .

Empirical
distribution

Bootstrap properties

The bootstrap estimate of mean

$$\hat{\theta}^*_{(\bullet)} = \frac{\hat{\theta}^*_1 + \hat{\theta}^*_2 + \ldots + \hat{\theta}^*_B}{B},$$

$$\widehat{bias} = \hat{\theta}^*_{(\bullet)} - \hat{\theta} = \hat{\theta}^*_{(\bullet)} - \bar{X} \xrightarrow[B \to \infty]{} 0$$

Problem: Prove asymptotic unbiasness.

MATLAB function

```
boot=inline('x(unidrnd(length(x),m,length(x)))','x',
'm')

X=[5 8 3 2]

>>bs=boot(X,3)

bs =
```

2	5	2	3
5	2	2	3
2	3	5	8

3 replicates
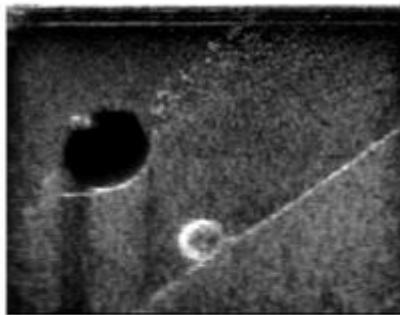
**bootstat = bootstrp(nboot,bootfun,d1,...)**
draws nboot bootstrap data samples, computes statistics on
each sample using bootfun, and returns the results in the
matrix bootstat.nboot

Limitation
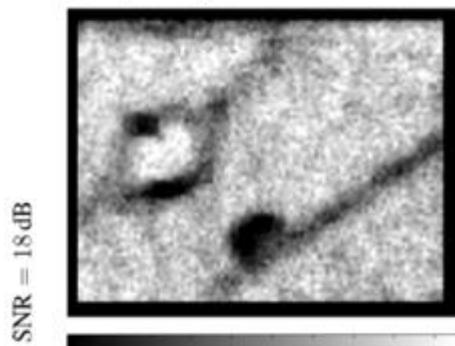
Bootstrap resampling assumes i.i.d. data. If observations are NOT independent and identically distributed, you need a different sampling strategy.

This is why bootstrap method is *rarely* used in images.
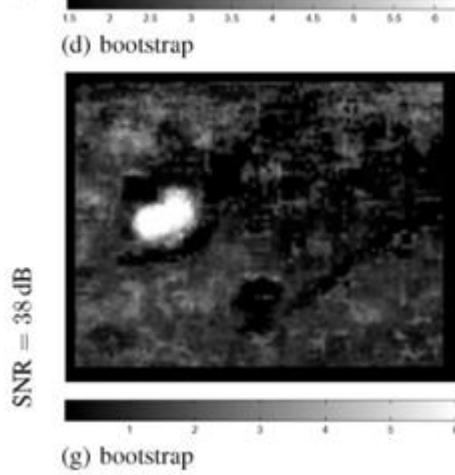
Block bootstrap on images

(a) input image

SNR = 18 dB

(d) bootstrap

SNR = 38 dB

(g) bootstrap

Can be used to estimate the performance of image registration when there is no ground truth. The residual of the model fit is block bootrapped.

Kybic, J. 2010 IEEE Trans. Image Processing 19:64-73

Question: This this a good validation method or not?

→Topology invariant resampling
Resampling is done in the spectral domain

Wang et al. 2018 Annals of Applied Stat.

References on bootstrap

Davison and Hinkley, Bootstrap Methods and their Application

Efron and Gong (1983) A Leisurely Look at the Bootstrap, American Statistician

Efron and Tibshirani (1986) Bootstrap Methods for Standard Errors, Statistical Science

Derrig, Ostaszewski, Rempala (2000) Applications of Resampling Methods in Actuarial Practice, PCAS

B. Efron (1979) Computers and the theory of statistics: thinking the unthinkable, SIAM Review, 21, 460-480.

B. Efron and R. J. Tibshirani (1993) An Introduction to the Bootstrap. Chapman & Hall.

J. I. De la Rosa and G. A. Fleury (2006) Bootstrap methods for a measurement estimation problem. IEEE Transactions on Instrumentation and Measurement, 55, 3, 820–827.

Unit Outcome

Permutation resampling

1) Able to enumerate permutations
2) Able to numerically generate permutations of images
3) Able to perform permutation test

Self assessment questions

1) Redo the permutation test example in MATLAB demo with a different example and the Gaussian kernel smoothing method.

2) Design a permutation test procedure for paired vector data testing for the equivalence of paired data