Birds of a feather flock together

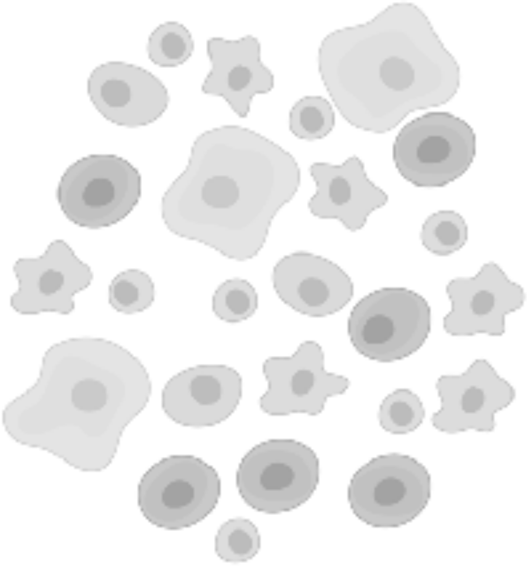
Clusters

Susan Holmes Wolfgang Huber Laura Symul October 9,2019

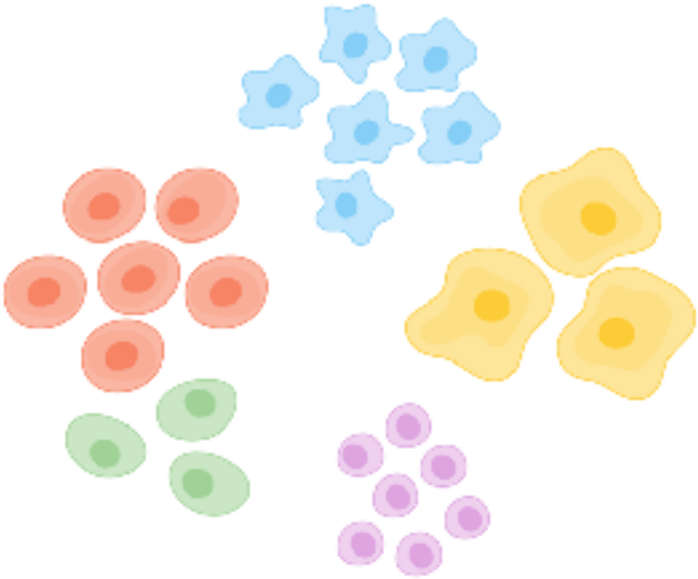
cc-by-sa/2.0 - Starlings near Sandfield,... by Brian Richard Marshall - geograph.org.uk/p/108850

Clustering =
Finding a latent or hidden variable which is not necessarily provided/accessible

Clusters =
Groups in the population (of individuals, cells, gene expression profiles) in which the **individual elements are similar to each others** and **different from the elements of other groups**.



Some **measurements**
(imaging, single cell RNA-seq, etc.)

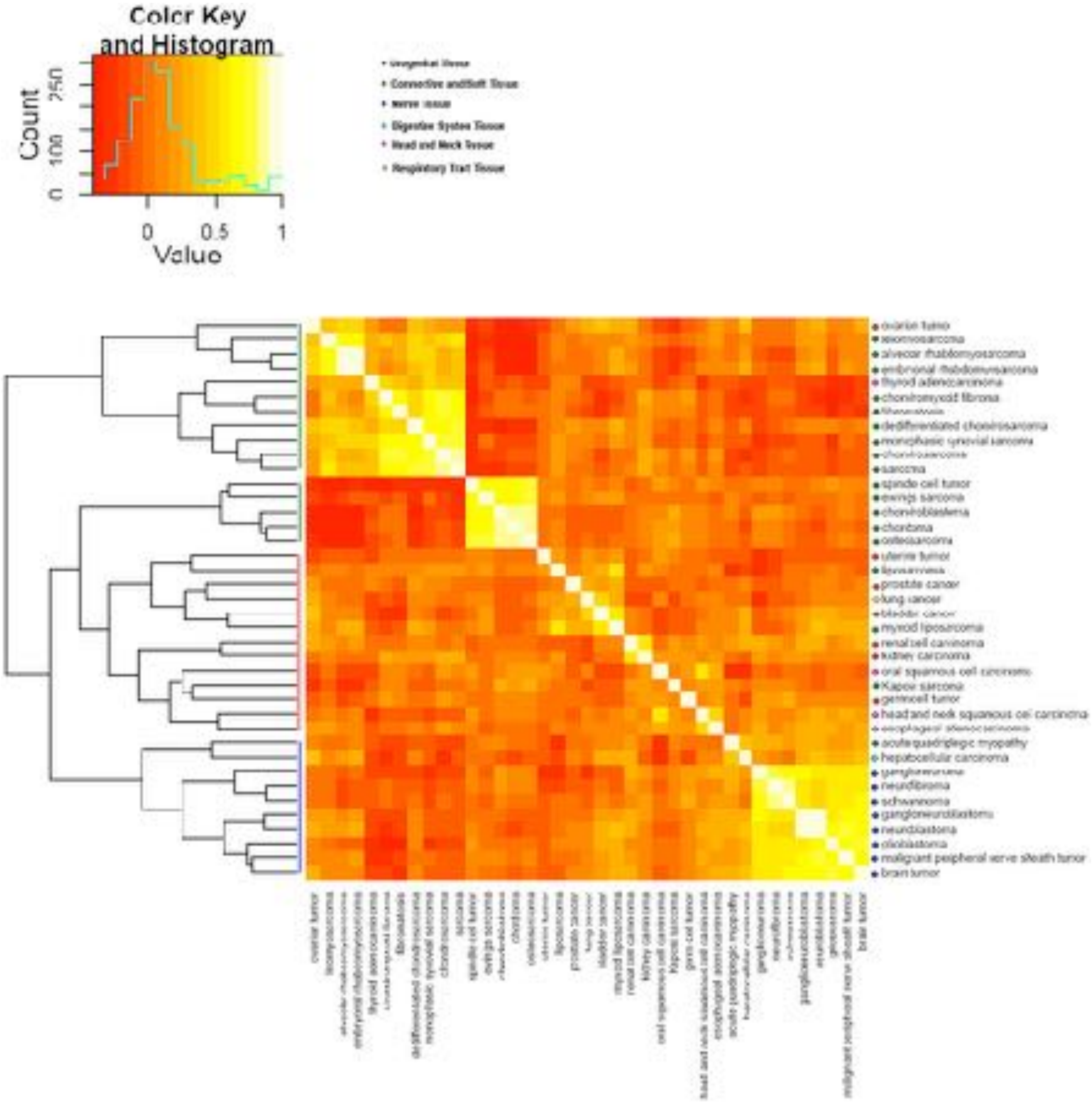


Groups = cell types

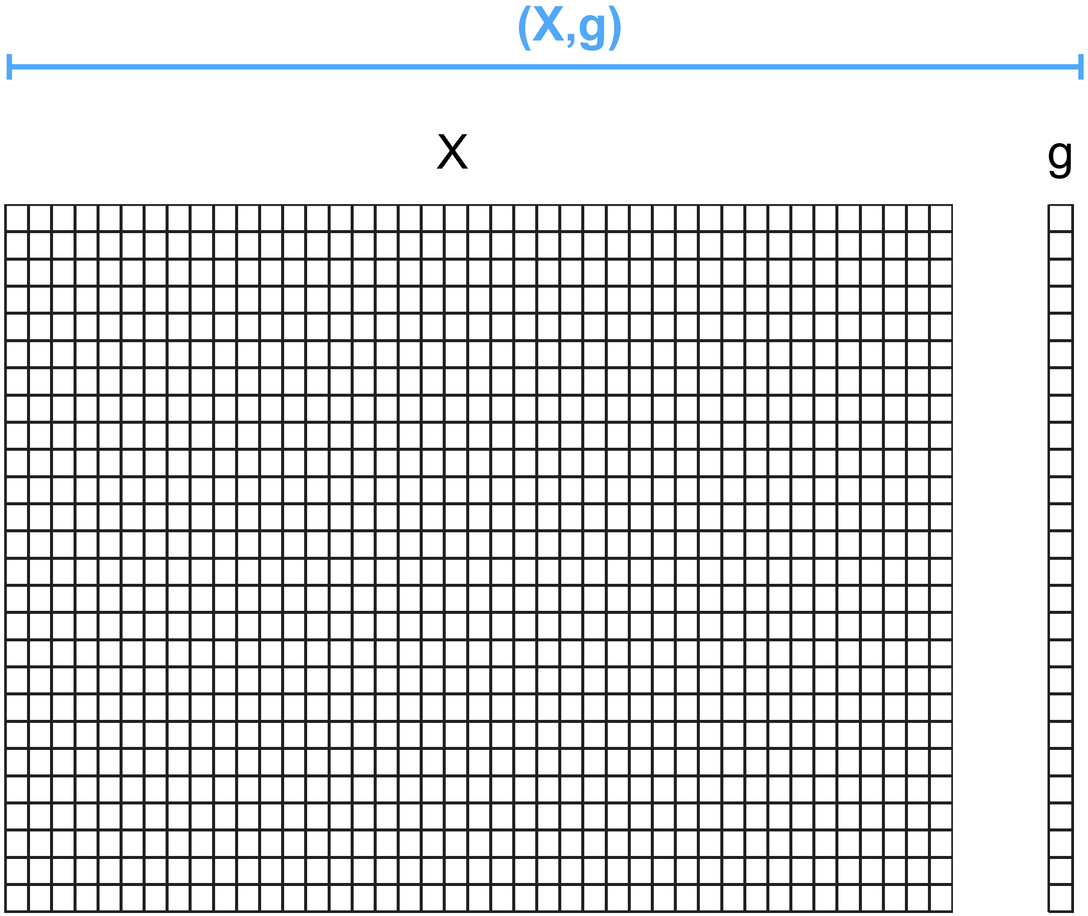
What is the central statistical concept behind any clustering?

Metric of (dis)similarity : a distance

Clusters frequently occur in biology.
Cell type, tissue, tumor type, ethnicities, etc.



Data Augmentation is the aim of clustering



data augmentation methods are methods that add useful but unknown components to the data

Goals for this lecture

1. Review measures of **(dis)similarity** that help us define clusters.

2. Explain **non-parametric methods** such as ***k-means*** or ***k-medoids***

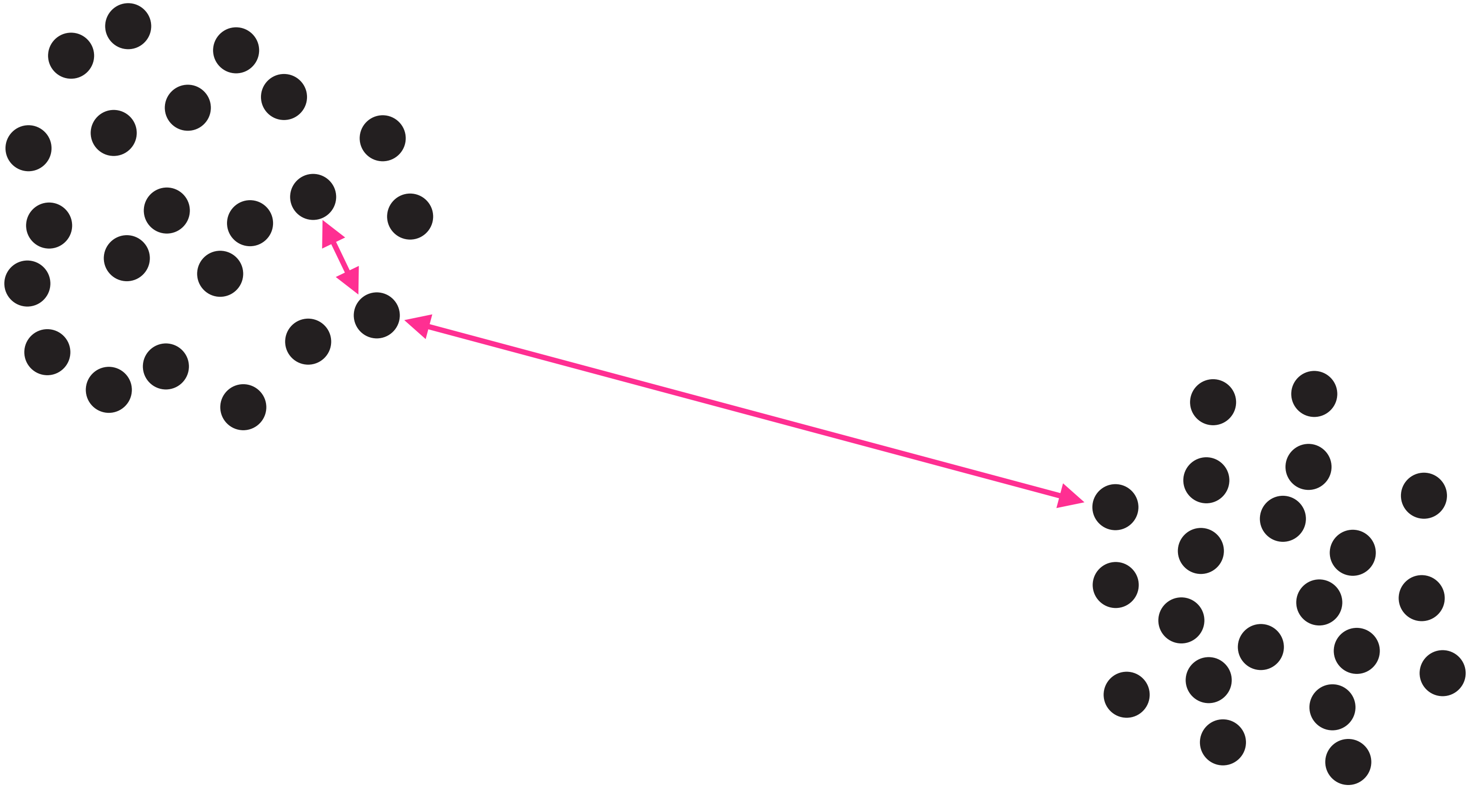
3. Explain the **recursive approach** to clustering that combines observations and groups into a hierarchy of sets and called ***hierarchical clustering***.

4. Understand how to **validate the clusters** and select the **optimal number of clusters**.

How (dis)similar are 2 elements?

(dis)similarity measure = **distance**

How (dis)similar are 2 elements?



How (dis)similar are 2 elements?

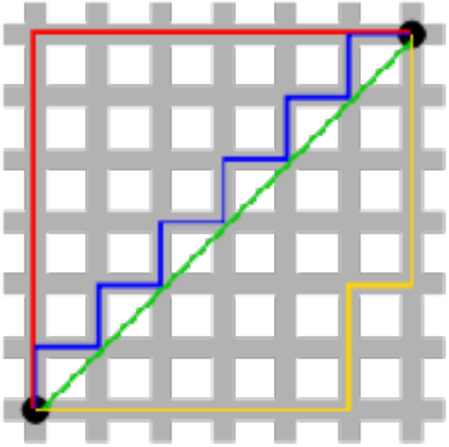
010001001001

001001001001

001001001001

110110110110

The choice or definition of **distance depends on the data**



Euclidean distance (L2)
$$d(A,B) = \sqrt{(a_1-b_1)^2 + (a_2-b_2)^2 + \ldots + (a_p-b_p)^2}.$$

Manhattan distance (L1)
$$d(A,B) = |a_1-b_1| + |a_2-b_2| + \ldots + |a_p-b_p|.$$

Maximum distance (L∞)
$$d_\infty(A,B) = \max_i |a_i - b_i|.$$

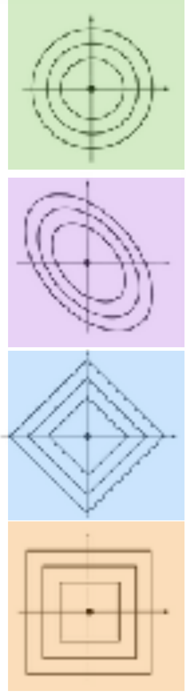
Minkowski distance (L*m*)
$$d(A,B) = ((a_1-b_1)^m + (a_2-b_2)^m + \ldots + (a_p-b_p)^m)^{\frac{1}{m}}.$$

Edit (Hamming) distance

Binary distance

Jaccard distance
$$d_J(S,T) = 1 - J(S,T) = \frac{f_{01}+f_{10}}{f_{01}+f_{10}+f_{11}}.$$

Correlation-based distance
$$d(A,B) = \sqrt{2(1-\mathrm{cor}(A,B))}.$$

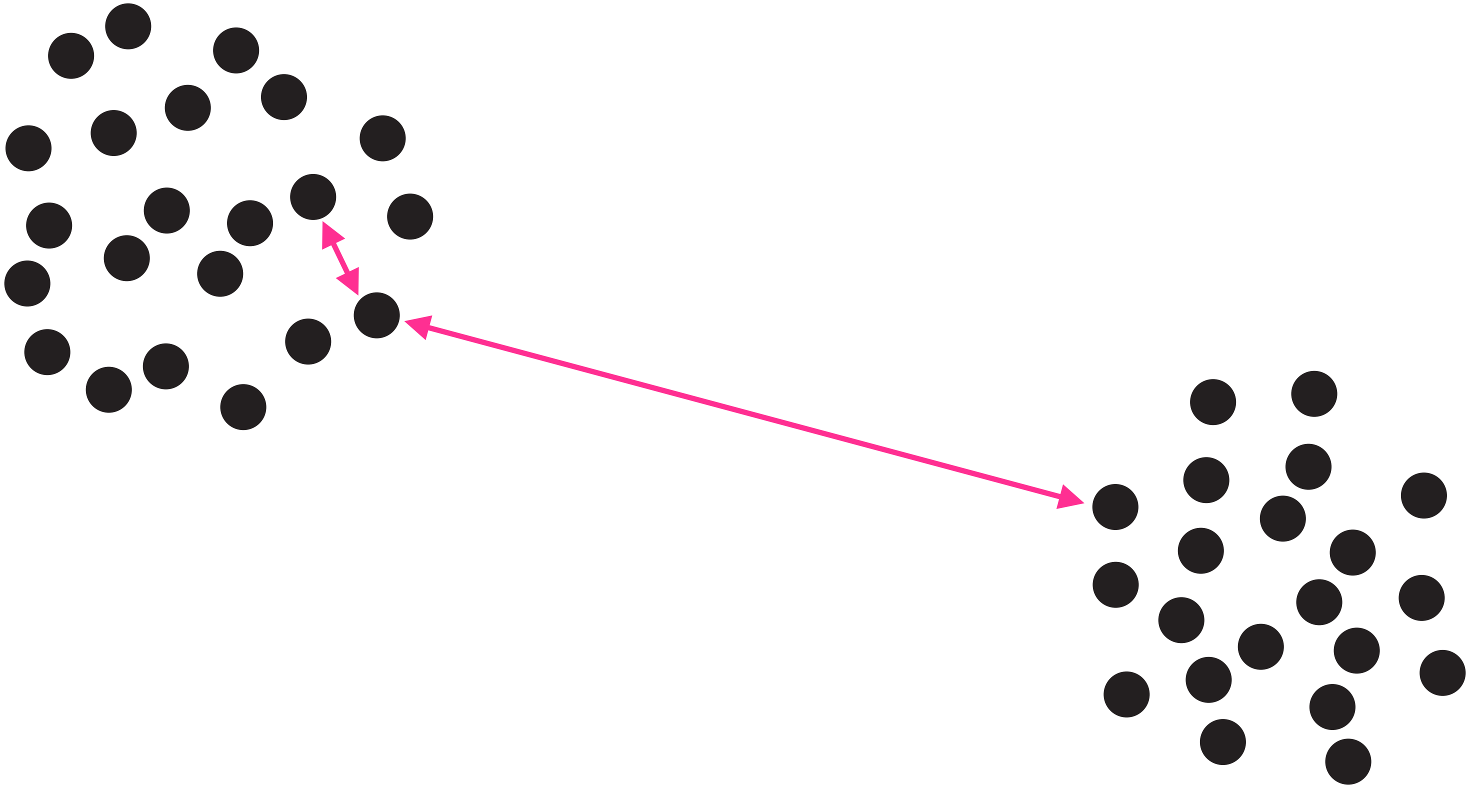


Weighted Euclidean distance

Mahalanobis distance

…

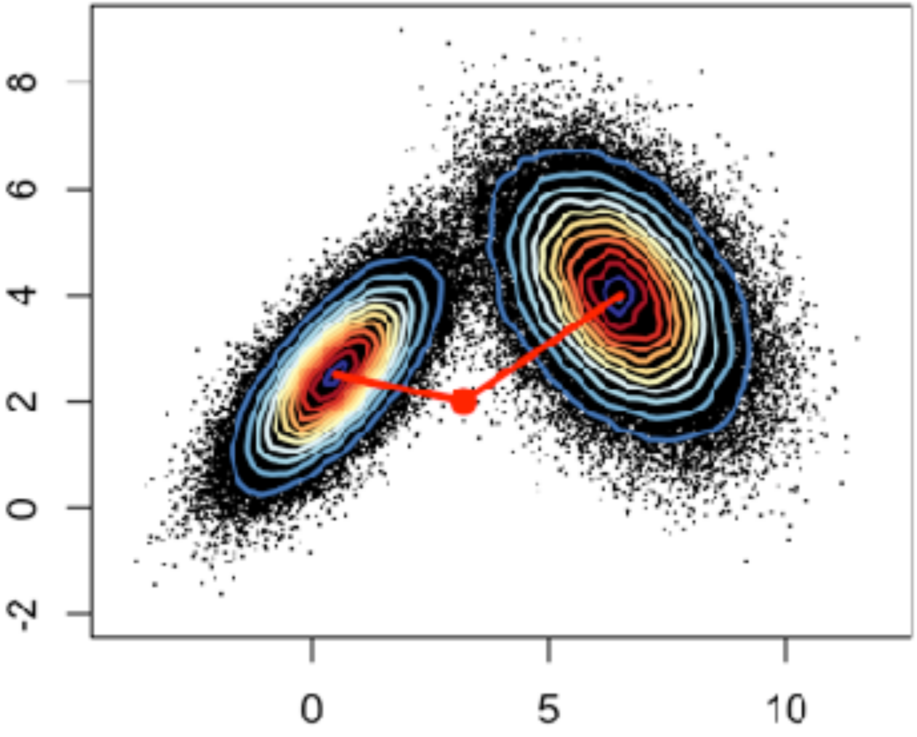
Euclidean distance



$$d(A, B) = \sqrt{(a_1 - b_1)^2 + (a_2 - b_2)^2 + \ldots + (a_p - b_p)^2}.$$

Weighted Euclidean distance

Is the **red point**, a “new” datapoint, closer to the cluster on the right or the cluster on the left?



The weight on the dimensions depends on the cluster

Binary distance

```
010001001001
001001001001
------------
001001001001
110110110110
```

$$1- \frac{\text{The sum of elements that are the same}}{\text{The number of elements}}$$

Jaccard distance

010001001001

001001001001

001001001001

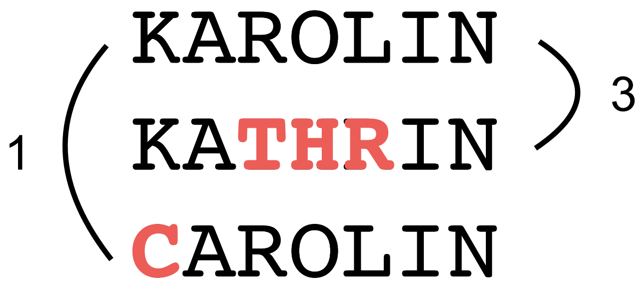
110110110110

The **co-occurrence** is more important than the co-absence

$$1- \frac{\text{The sum of 1's that overlap}}{\text{The union of 1's}}$$

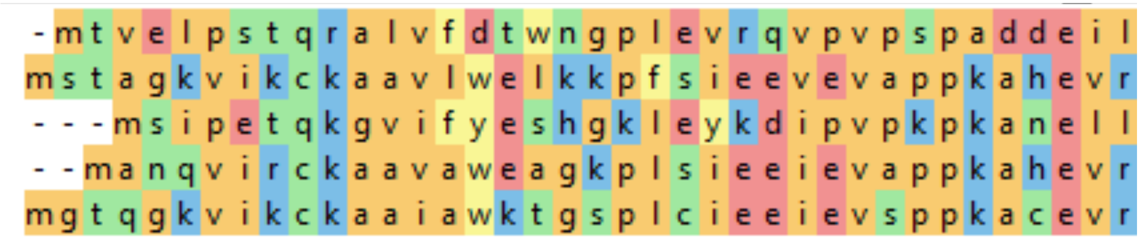
Initially developed for ecological data for the occurrence of traits or features

Edit (Hamming) distance



The number of edits that needs to be done.

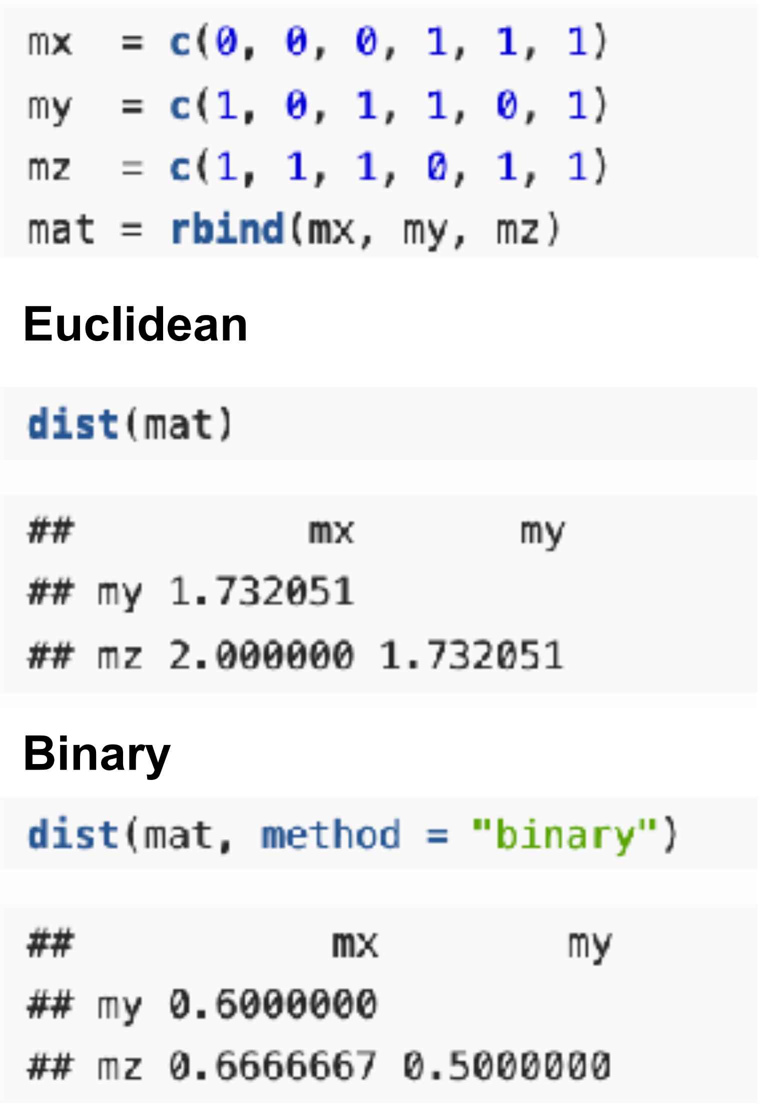
This could be applied to nucleotide or amino acid sequences…



```
-mtvelpstqralvfdtwngplevrqvpvpspaddeil
mstagkvikckaavlwelkkpfsieevevappkahevr
---msipetqkgvifyeshgkleykdipvpkpkanell
--manqvirckaavaweagkplsieeievappkahevr
mgtqgkvikckaaiawktgsplcieeievsppkacevr
```

…although in that case, the **different character substitutions** are usually associated with **different contributions to the distance** (to account for physical or evolutionary similarity), and **deletions and insertions** may also be allowed

Distances in R



```r
mx  = c(0, 0, 0, 1, 1, 1)
my  = c(1, 0, 1, 1, 0, 1)
mz  = c(1, 1, 1, 0, 1, 1)
mat = rbind(mx, my, mz)
```

Euclidean

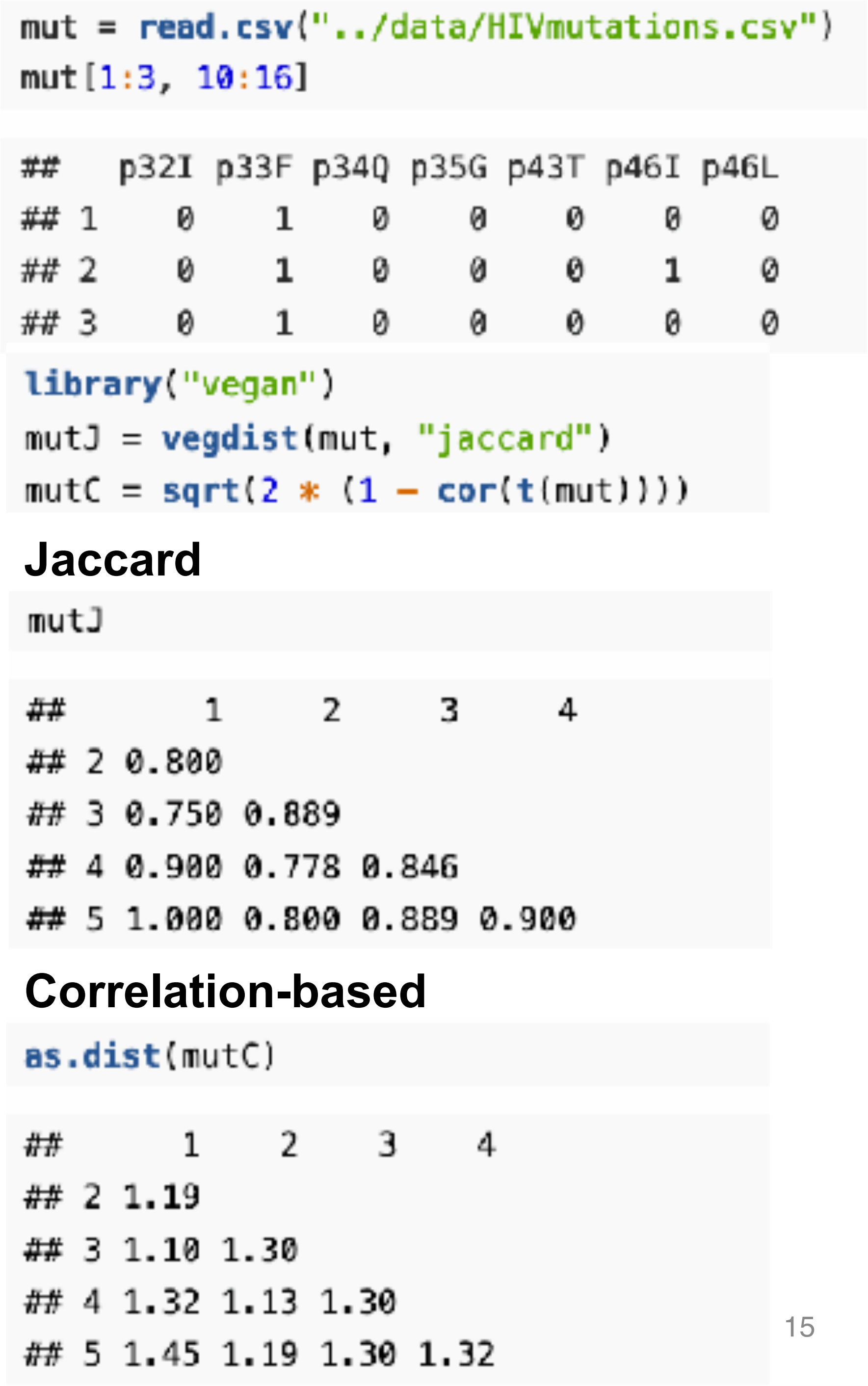
```r
dist(mat)
```

```
##          mx       my
## my 1.732051
## mz 2.000000 1.732051
```

Binary

```r
dist(mat, method = "binary")
```

```
##           mx        my
## my 0.6000000
## mz 0.6666667 0.5000000
```



```r
mut = read.csv("../data/HIVmutations.csv")
mut[1:3, 10:16]
```

```
##   p32I p33F p34Q p35G p43T p46I p46L
## 1    0    1    0    0    0    0    0
## 2    0    1    0    0    0    1    0
## 3    0    1    0    0    0    0    0
```

```r
library("vegan")
mutJ = vegdist(mut, "jaccard")
mutC = sqrt(2 * (1 - cor(t(mut))))
```

Jaccard

```r
mutJ
```

```
##       1     2     3     4
## 2 0.800
## 3 0.750 0.889
## 4 0.900 0.778 0.846
## 5 1.000 0.800 0.889 0.900
```

Correlation-based

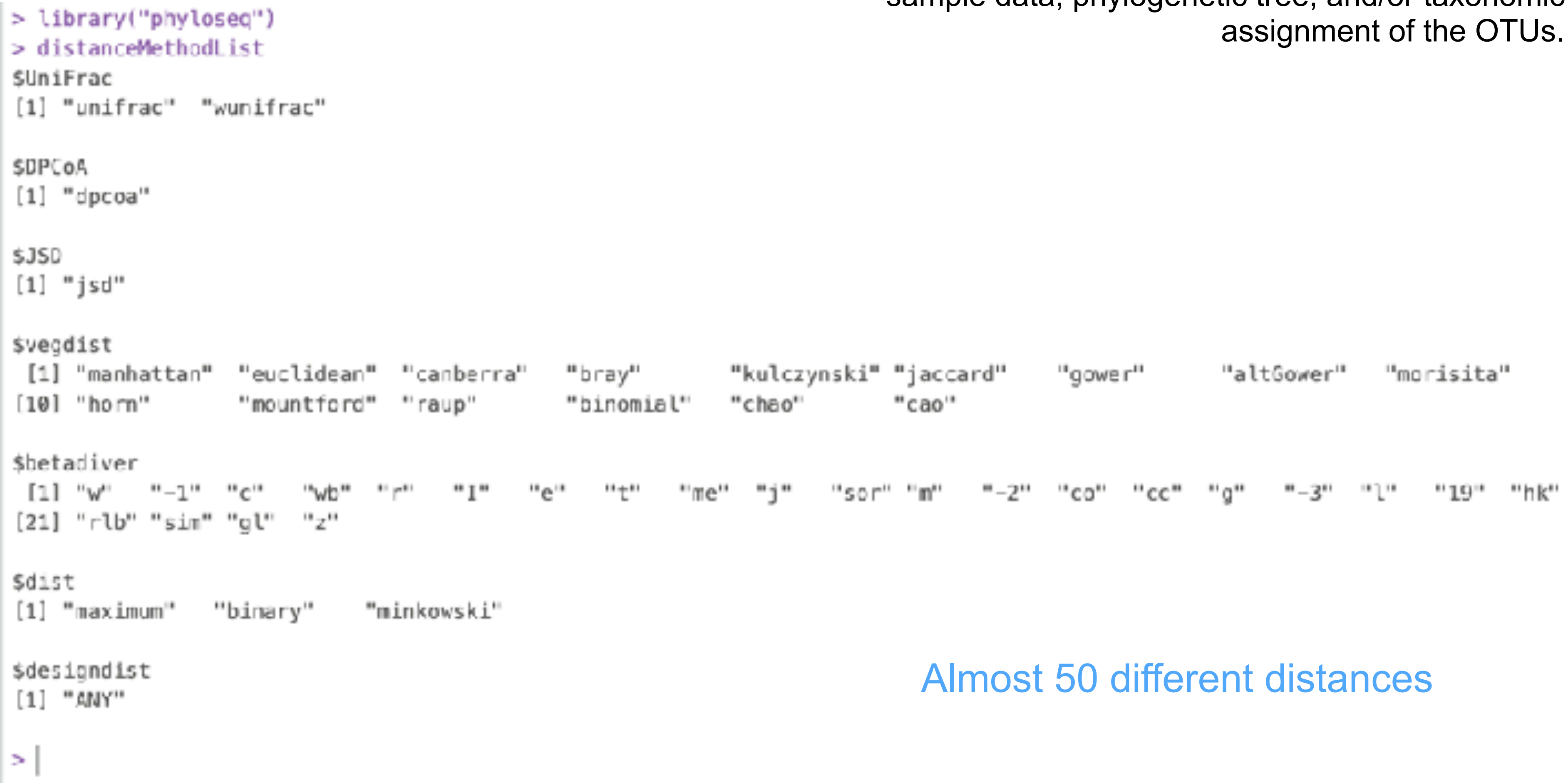
```r
as.dist(mutC)
```

```
##      1    2    3    4
## 2 1.19
## 3 1.10 1.30
## 4 1.32 1.13 1.30
## 5 1.45 1.19 1.30 1.32
```

Distances in R
phyloseq package

phyloseq: analyze microbiome census data using R

The phyloseq package is a tool to import, store, analyze, and graphically display complex phylogenetic sequencing data that has already been clustered into Operational Taxonomic Units (OTUs), especially when there is associated sample data, phylogenetic tree, and/or taxonomic assignment of the OTUs.

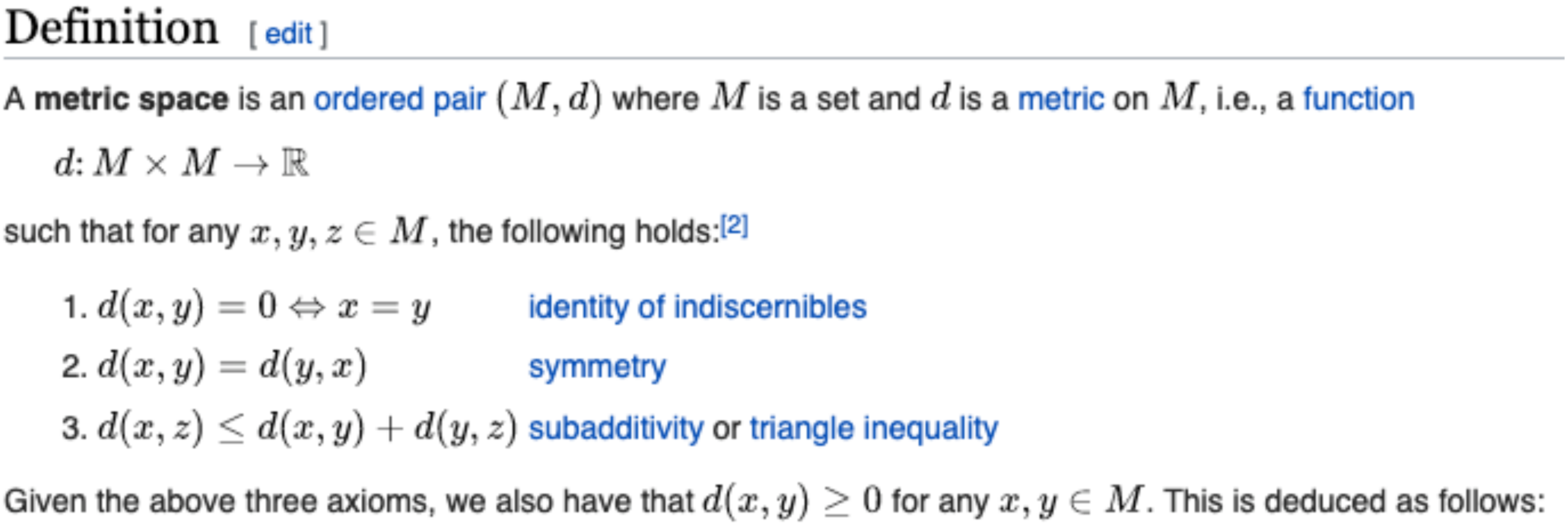


```
> library("phyloseq")
> distanceMethodList
$UniFrac
[1] "unifrac"  "wunifrac"

$DPCoA
[1] "dpcoa"

$JSD
[1] "jsd"

$vegdist
 [1] "manhattan"  "euclidean"  "canberra"   "bray"       "kulczynski" "jaccard"    "gower"      "altGower"   "morisita"
[10] "horn"       "mountford"  "raup"       "binomial"   "chao"       "cao"

$betadiver
 [1] "w"   "-1"  "c"   "wb"  "r"   "I"   "e"   "t"   "me"  "j"   "sor" "m"   "-2"  "co"  "cc"  "g"   "-3"  "l"   "19"  "hk"
[21] "rlb" "sim" "gl"  "z"

$dist
[1] "maximum"   "binary"    "minkowski"

$designdist
[1] "ANY"

> |
```

Almost 50 different distances

http://joey711.github.io/phyloseq/distance.html

If you **really** need to define a **new distance**, it must…



Definition [edit]

A **metric space** is an ordered pair (M, d) where M is a set and d is a metric on M, i.e., a function

$$d\colon M \times M \to \mathbb{R}$$

such that for any $x, y, z \in M$, the following holds:[2]

1. $d(x, y) = 0 \Leftrightarrow x = y$ identity of indiscernibles
2. $d(x, y) = d(y, x)$ symmetry
3. $d(x, z) \leq d(x, y) + d(y, z)$ subadditivity or triangle inequality

Given the above three axioms, we also have that $d(x, y) \geq 0$ for any $x, y \in M$. This is deduced as follows:

https://en.wikipedia.org/wiki/Metric_space

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Non-parametric clustering methods (k-methods, top-down)

k-medoids

PAM (Partitioning **A**round (k) **M**edoids**)**

k-means

1. Starts from a matrix of p features measured on a set of n observations.

2. **Randomly pick** k **distinct cluster centers** out of the n observations ("seeds").

3. **Assign each of the** remaining **observations** to the group to whose center it is the closest.

4. **For each group, choose a new center** from the observations in the group, such that the sum of the distances of group members to the center is minimal; this is called the ***medoid***.

5. **Repeat** Steps 3 and 4 **until the groups stabilize**.

http://shabal.in/visuals/kmeans/4.html

Non-parametric clustering methods
(k-methods, top-down)

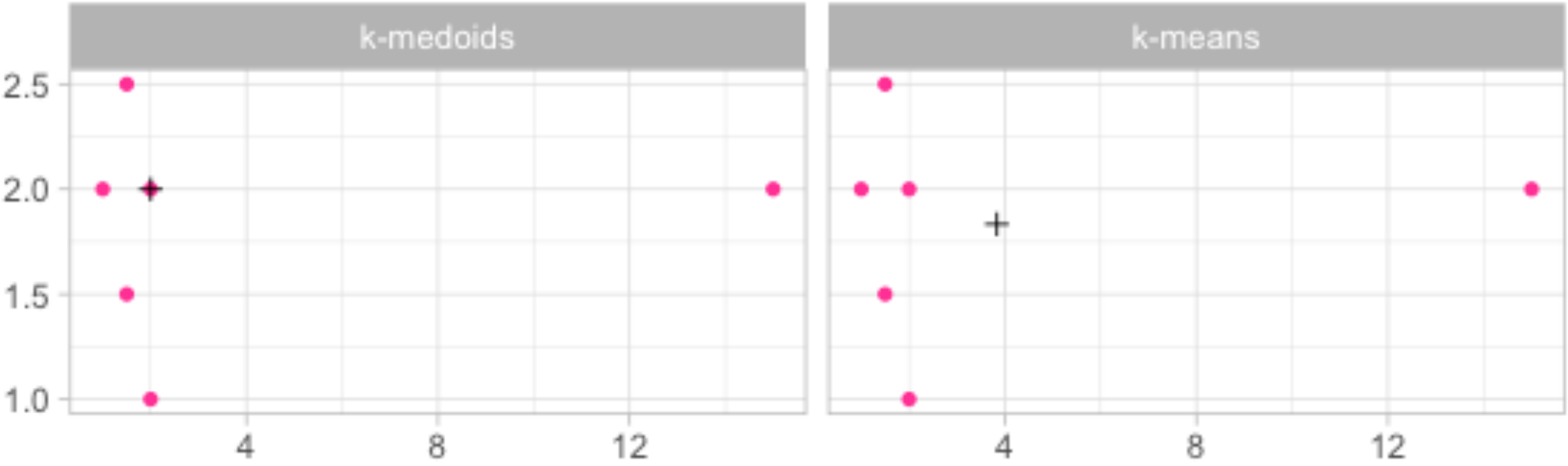
The difference between k-medoids and k-means is at step 4, when choosing the new centers

k-medoids

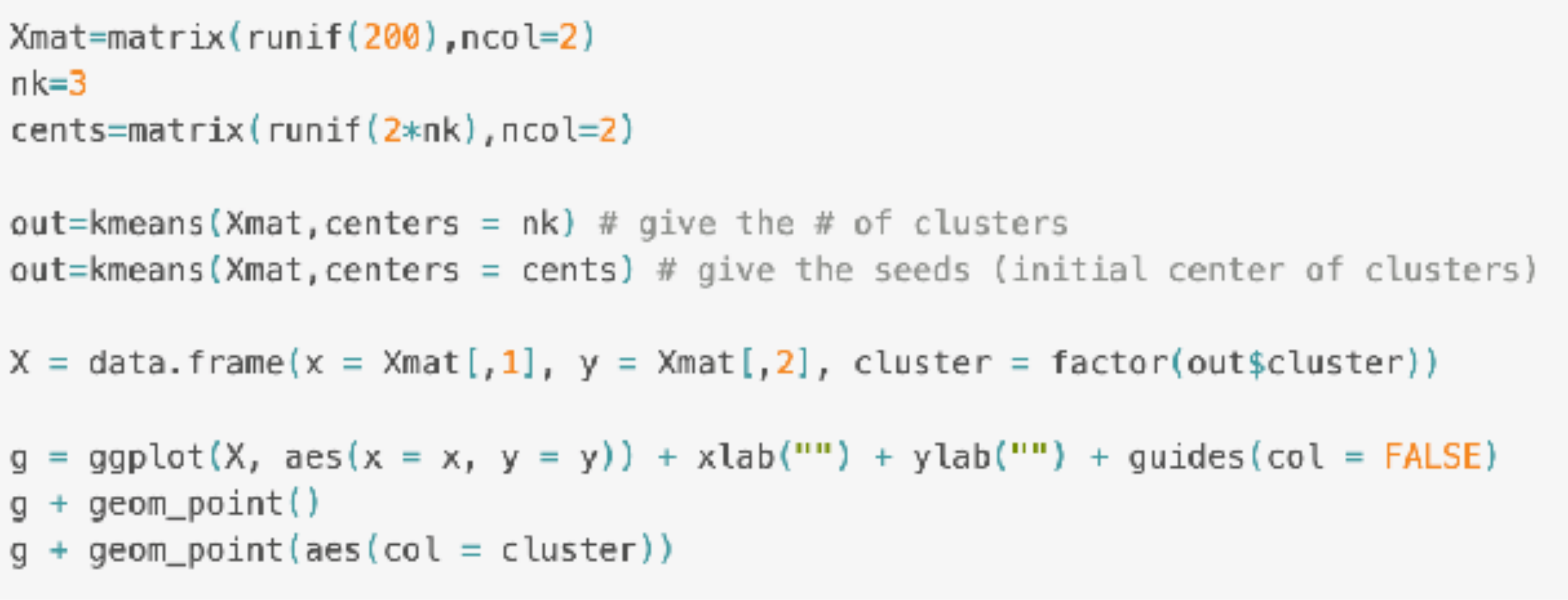
The new centers are selected **among the observations**

k-means

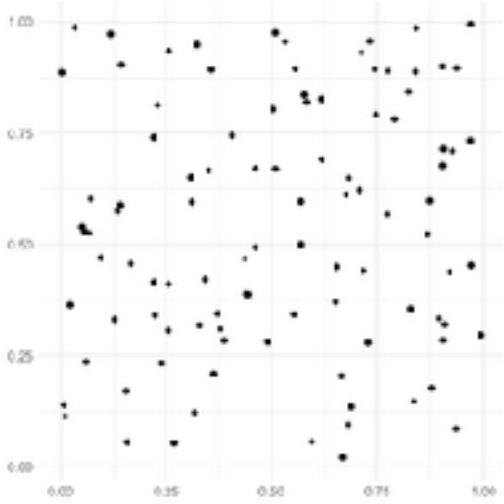
The new centers are **computed** as the **arithmetic mean** between the observations of each group

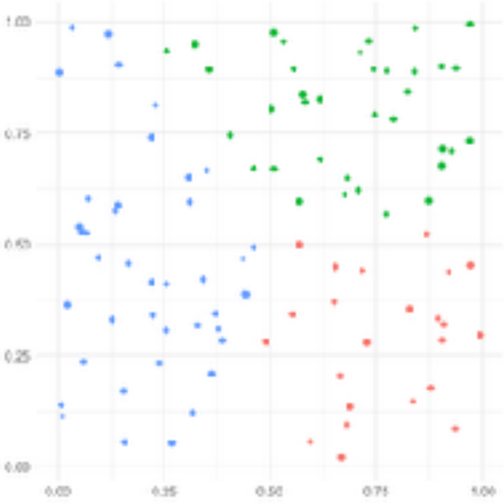


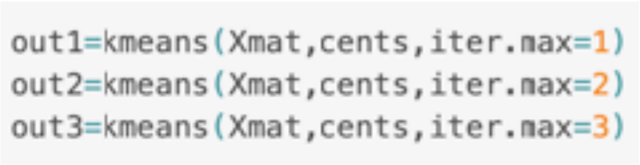
Non-parametric clustering methods
(k-methods, top-down)



```
Xmat=matrix(runif(200),ncol=2)
nk=3
cents=matrix(runif(2*nk),ncol=2)

out=kmeans(Xmat,centers = nk) # give the # of clusters
out=kmeans(Xmat,centers = cents) # give the seeds (initial center of clusters)

X = data.frame(x = Xmat[,1], y = Xmat[,2], cluster = factor(out$cluster))

g = ggplot(X, aes(x = x, y = y)) + xlab("") + ylab("") + guides(col = FALSE)
g + geom_point()
g + geom_point(aes(col = cluster))
```







```
out1=kmeans(Xmat,cents,iter.max=1)
out2=kmeans(Xmat,cents,iter.max=2)
out3=kmeans(Xmat,cents,iter.max=3)
```

Non-parametric clustering methods (k-methods, top-down)

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2. **Randomly pick k distinct cluster centers** out of the n observations (“seeds”).

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5. **Repeat** Steps 3 and 4 **until the groups stabilize**.

Is the method robust?
i.e. does it give always the same result?

How can we improve that?

http://shabal.in/visuals/kmeans/4.html

Strong Forms & Tight Clusters

Dynamical Clusters

Repeats the process many times with **different seeds** (initial centers)
to build `**strong forms**' which are groups of observations that end up in the same classes for most possible initial configurations.

Diday and Brito, 1989

Resampling

Repeats the process many times on subsamples of the dataset
to create `**tight clusters**' which are groups of observations that are almost always grouped together.

Tseng and Wong, 2015

In R, see package ***clusterExperiment***

Data preprocessing matters

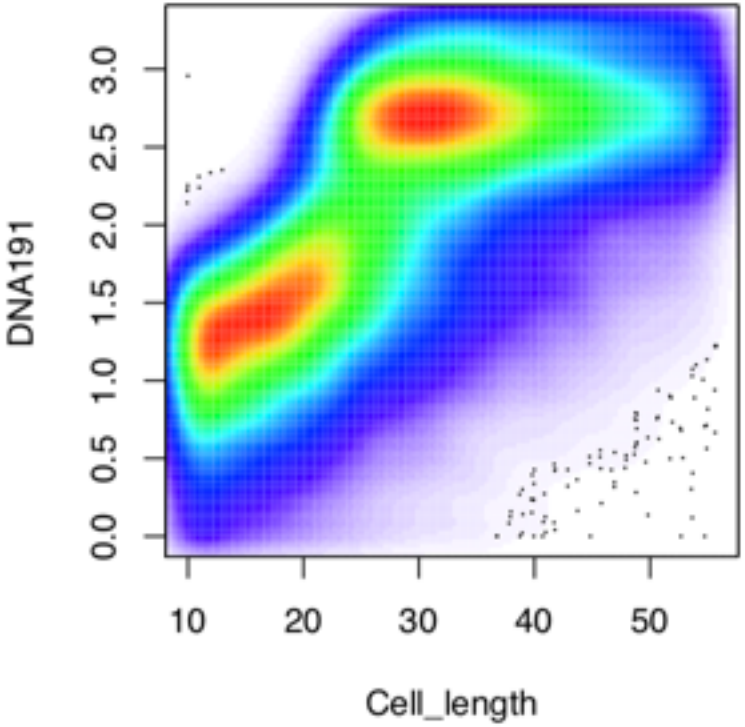
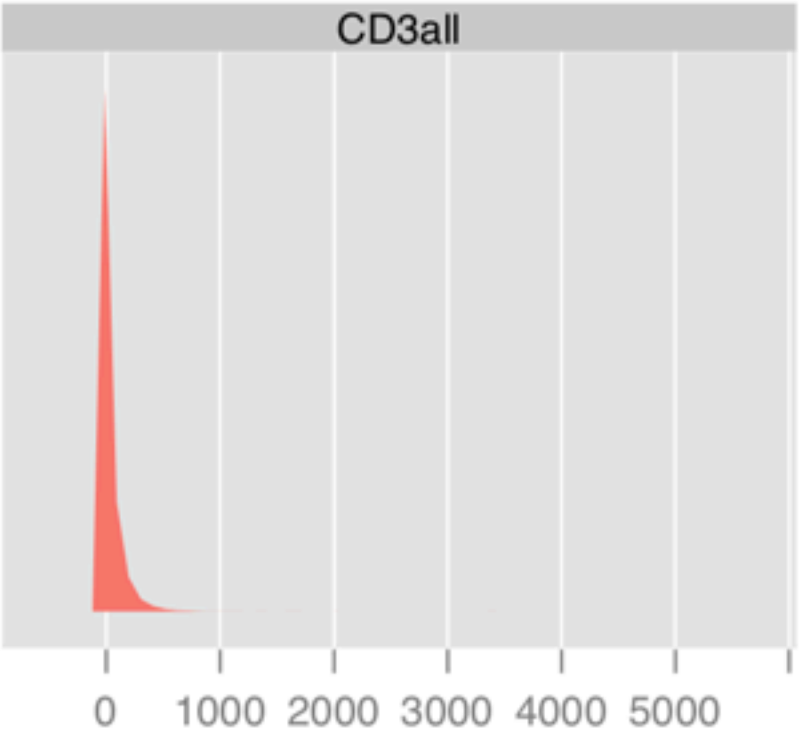


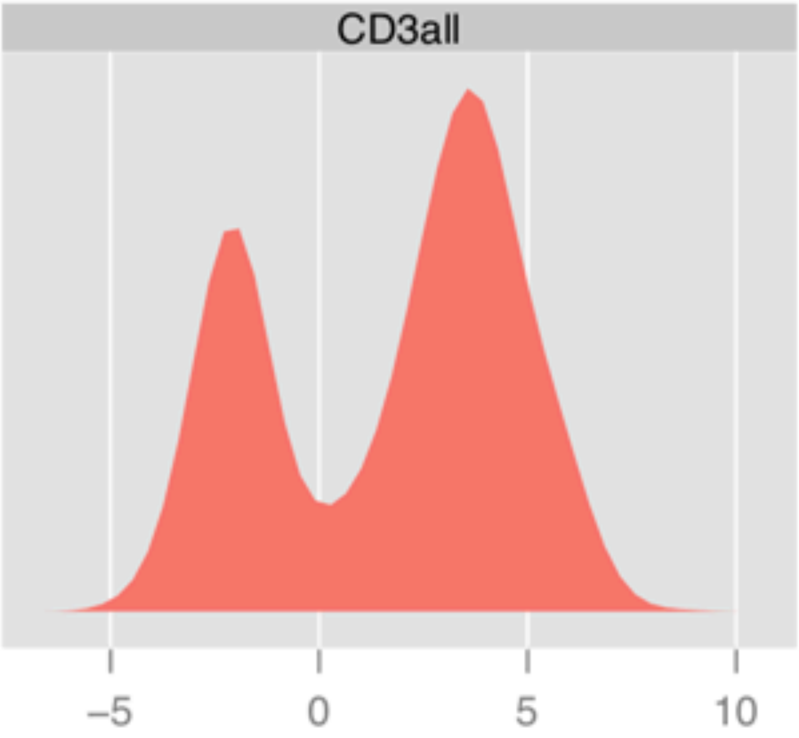
Figure 5.11: Cell measurements that show clear clustering in two dimensions.

Different scales

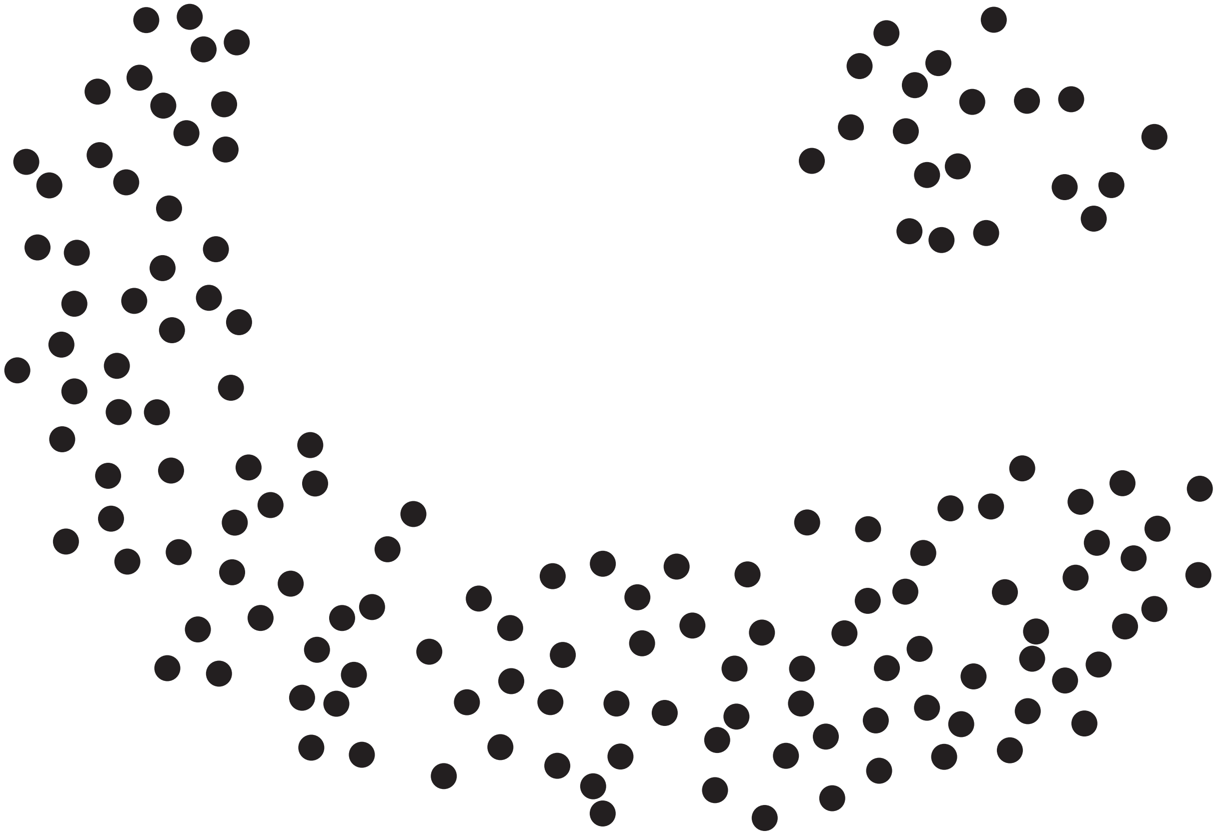
Raw



asinh



Density-based clustering



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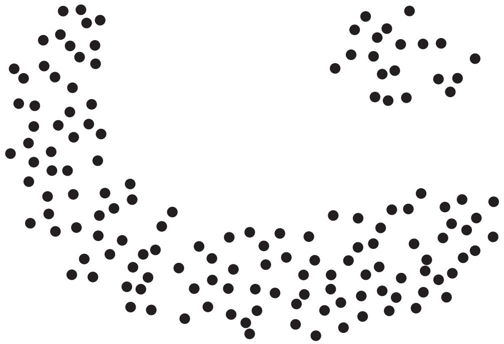


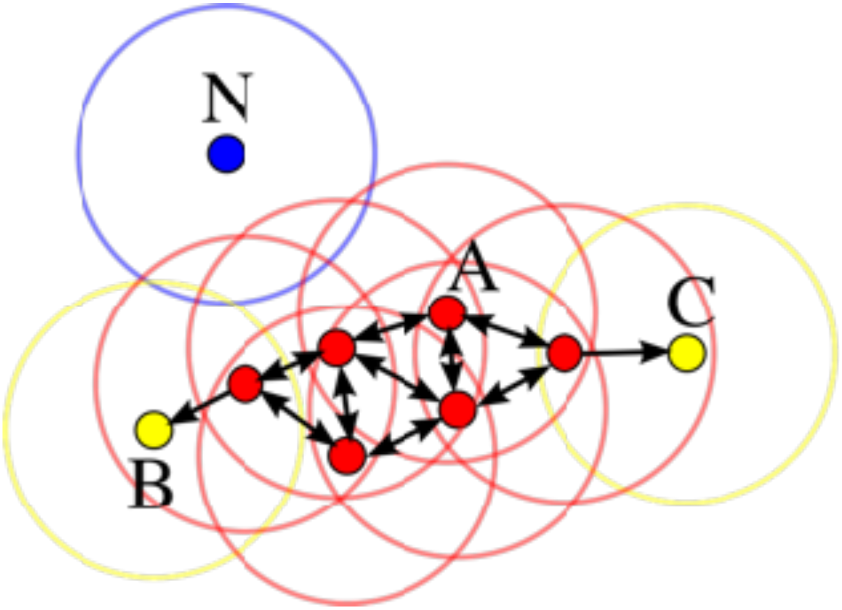
2 parameters:

Eps (ε) : the maximum distance between 2 points so that they are considered as “reachable” from one another

minPts: the minimum number of points for a cluster to be created.

It classifies each data-point into

- core points
- directly reachable points
- noise / outliers



Algorithm: **DBSCAN**
Density-**b**ased **s**patial **c**lustering
of **a**pplications with **n**oise

Martin Ester, Hans-Peter Kriegel, Jörg Sander and Xiaowei Xu,1996

Package and function dbscan in R

https://en.wikipedia.org/wiki/DBSCAN

How does density-based clustering (dbscan) work ?

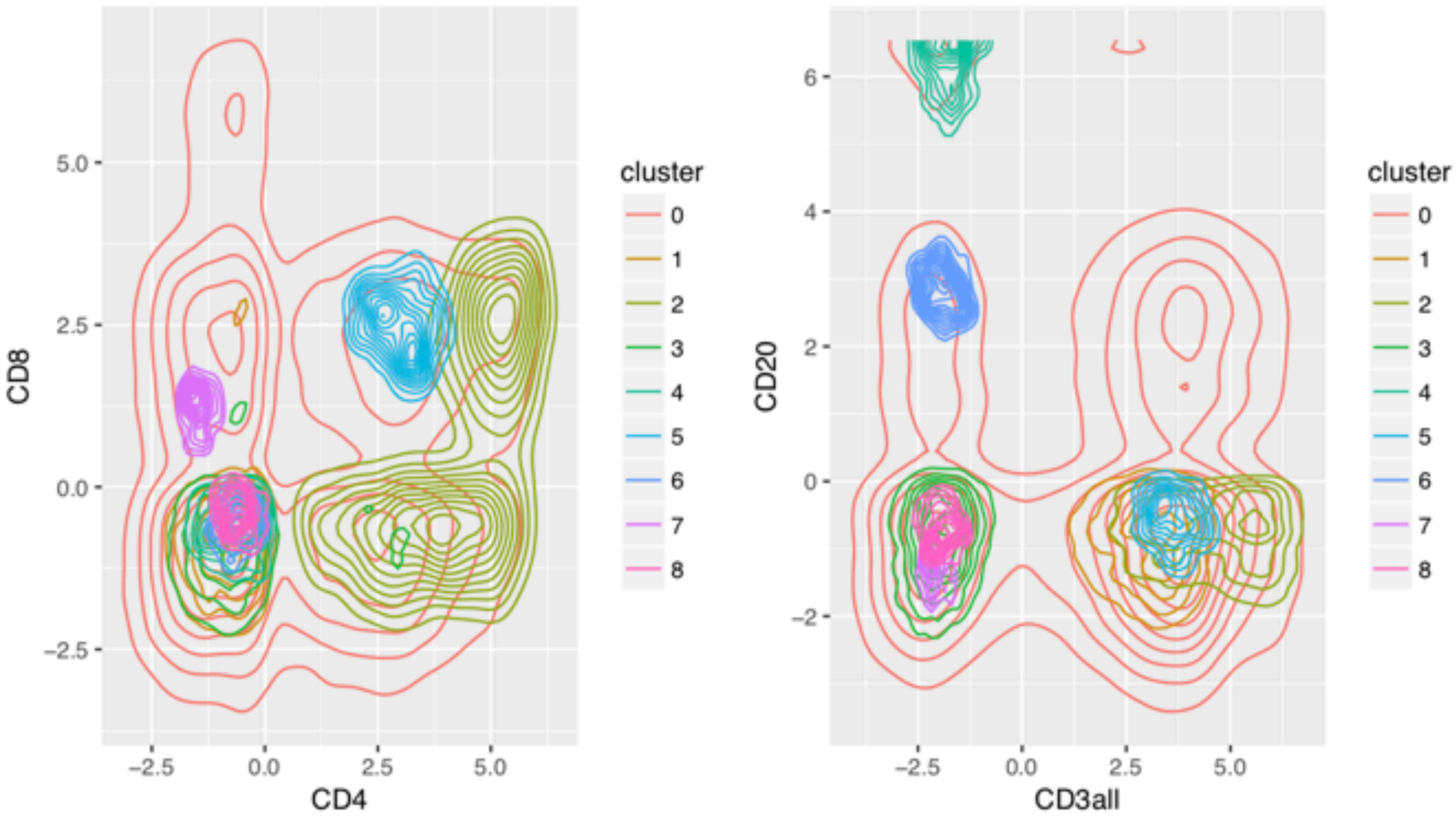
The dbscan method clusters points in dense regions according to the **density-connectedness** criterion. It looks at small neighborhood spheres of radius ϵ to see if points are connected.

The building block of dbscan is the concept of density-reachability: a point q is directly **density-reachable** from a point p if it is not further away than a given threshold ϵ, and if p is surrounded by sufficiently many points such that one may consider p (and q) be part of a dense region. We say that q is **density-reachable** from p if there is a sequence of points $p_1, \ldots, p_n$ with $p_1 = p$ and $p_n = q$, so that each p_{i+1} is directly density-reachable from p_i.

A **cluster** is then a subset of points that satisfy the following properties:

1. All points within the cluster are mutually density-connected.
2. If a point is density-connected to any point of the cluster, it is part of the cluster as well.
3. Groups of points must have at least `MinPts` points to count as a cluster.

Density-based clustering



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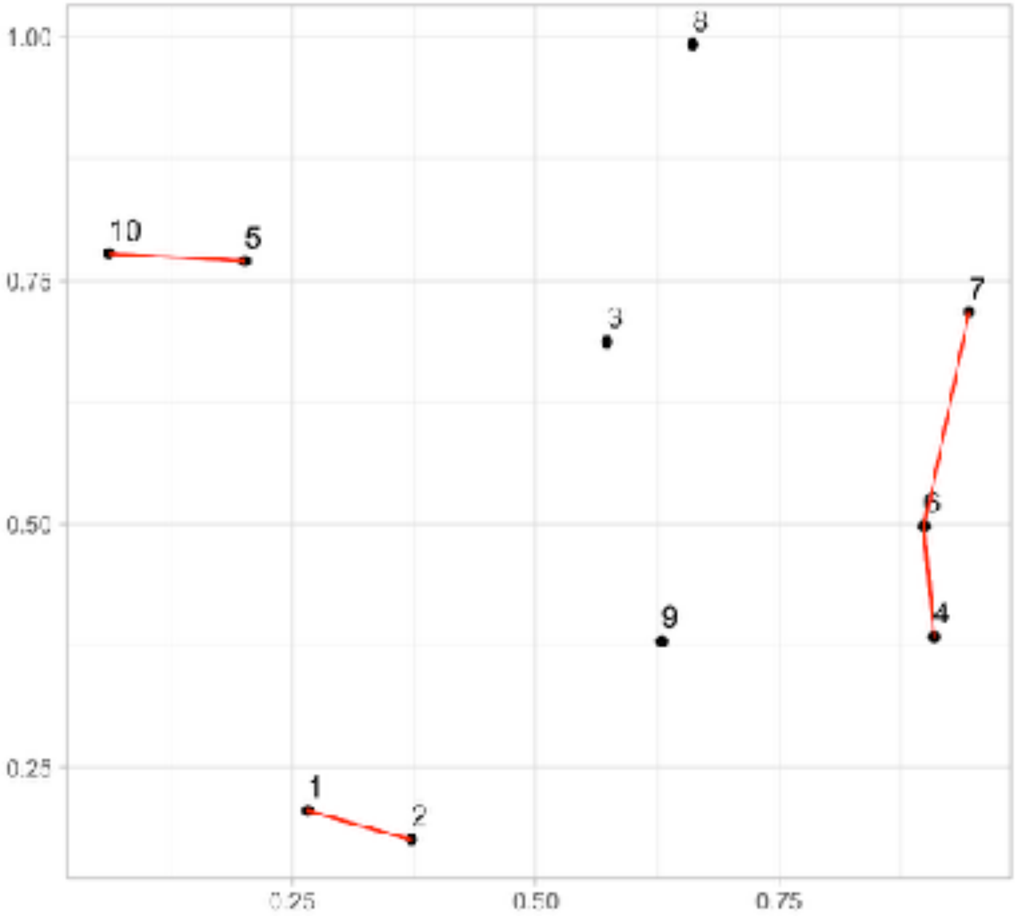
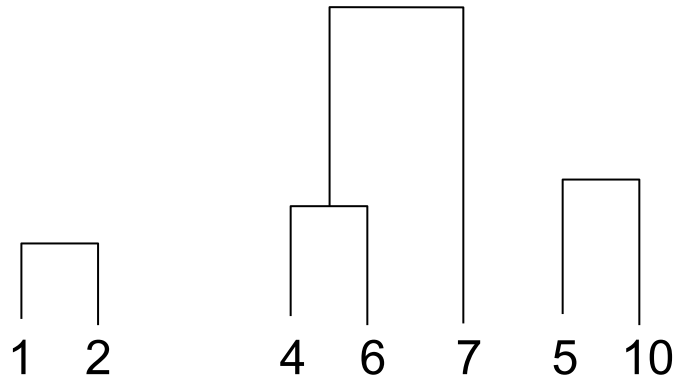
Hierarchical Clustering
(bottom-up)





Hierarchical Clustering
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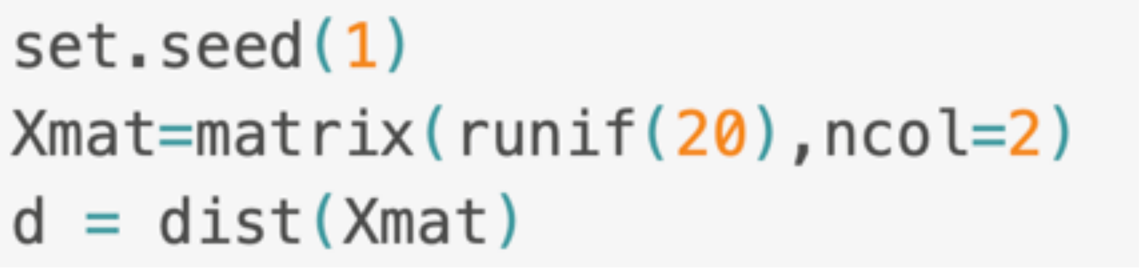
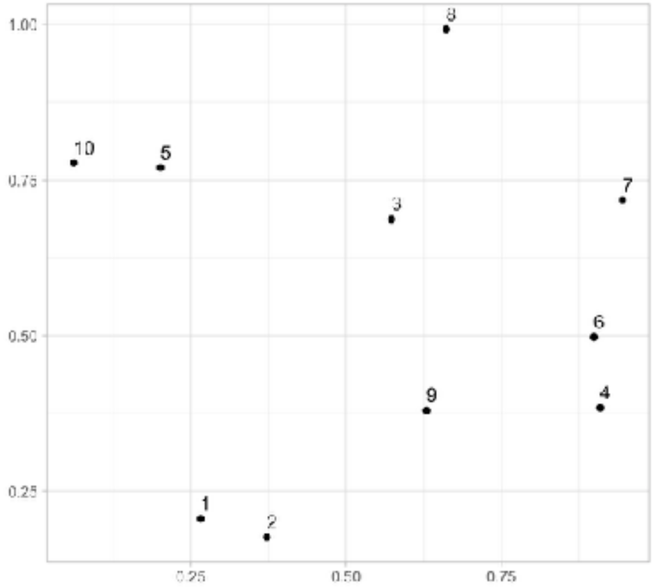
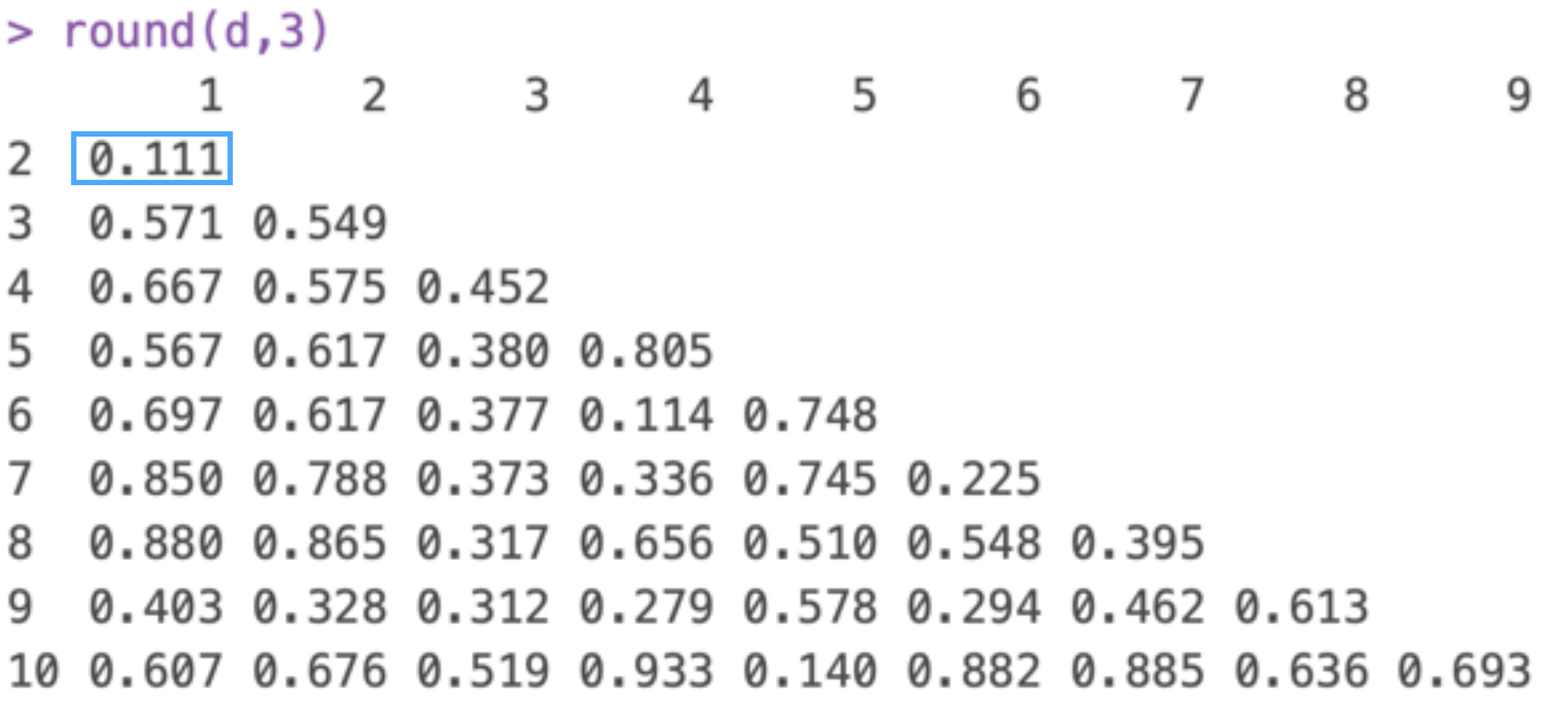


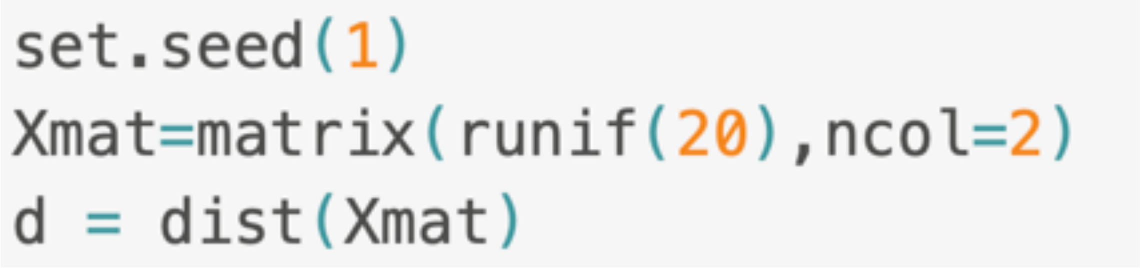
```
set.seed(1)
Xmat=matrix(runif(20),ncol=2)
d = dist(Xmat)
```





```
> round(d,3)
       1     2     3     4     5     6     7     8     9
2  0.111
3  0.571 0.549
4  0.667 0.575 0.452
5  0.567 0.617 0.380 0.805
6  0.697 0.617 0.377 0.114 0.748
7  0.850 0.788 0.373 0.336 0.745 0.225
8  0.880 0.865 0.317 0.656 0.510 0.548 0.395
9  0.403 0.328 0.312 0.279 0.578 0.294 0.462 0.613
10 0.607 0.676 0.519 0.933 0.140 0.882 0.885 0.636 0.693
```

Hierarchical Clustering
(bottom-up)



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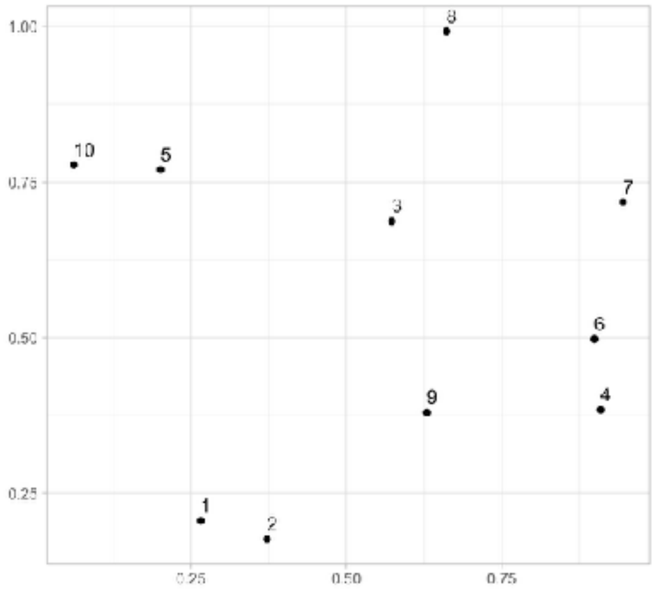
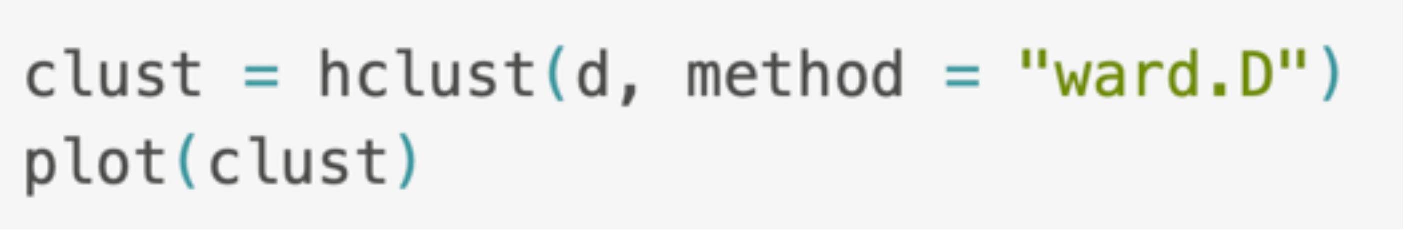
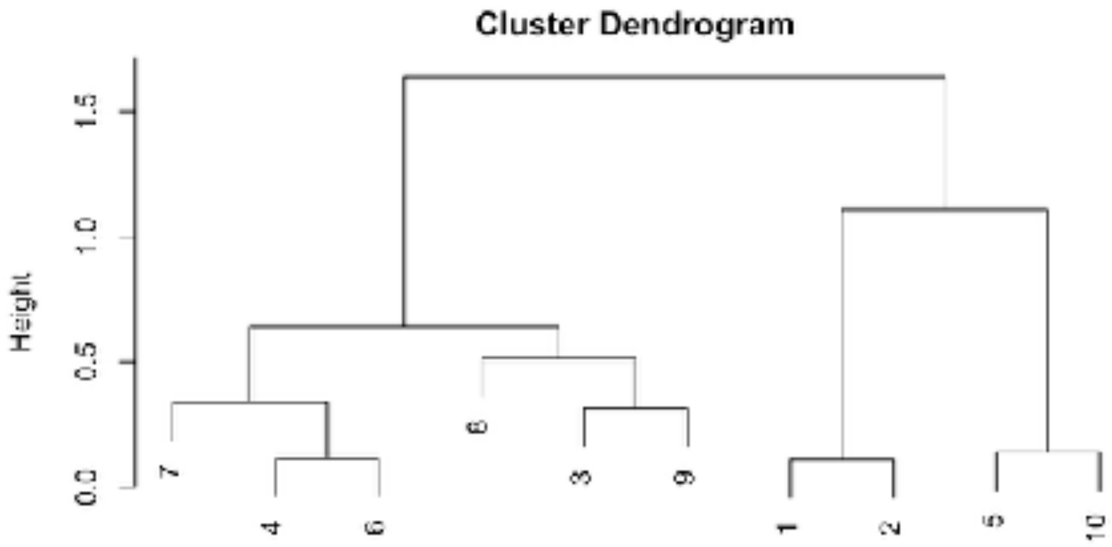




```
clust = hclust(d, method = "ward.D")
plot(clust)
```



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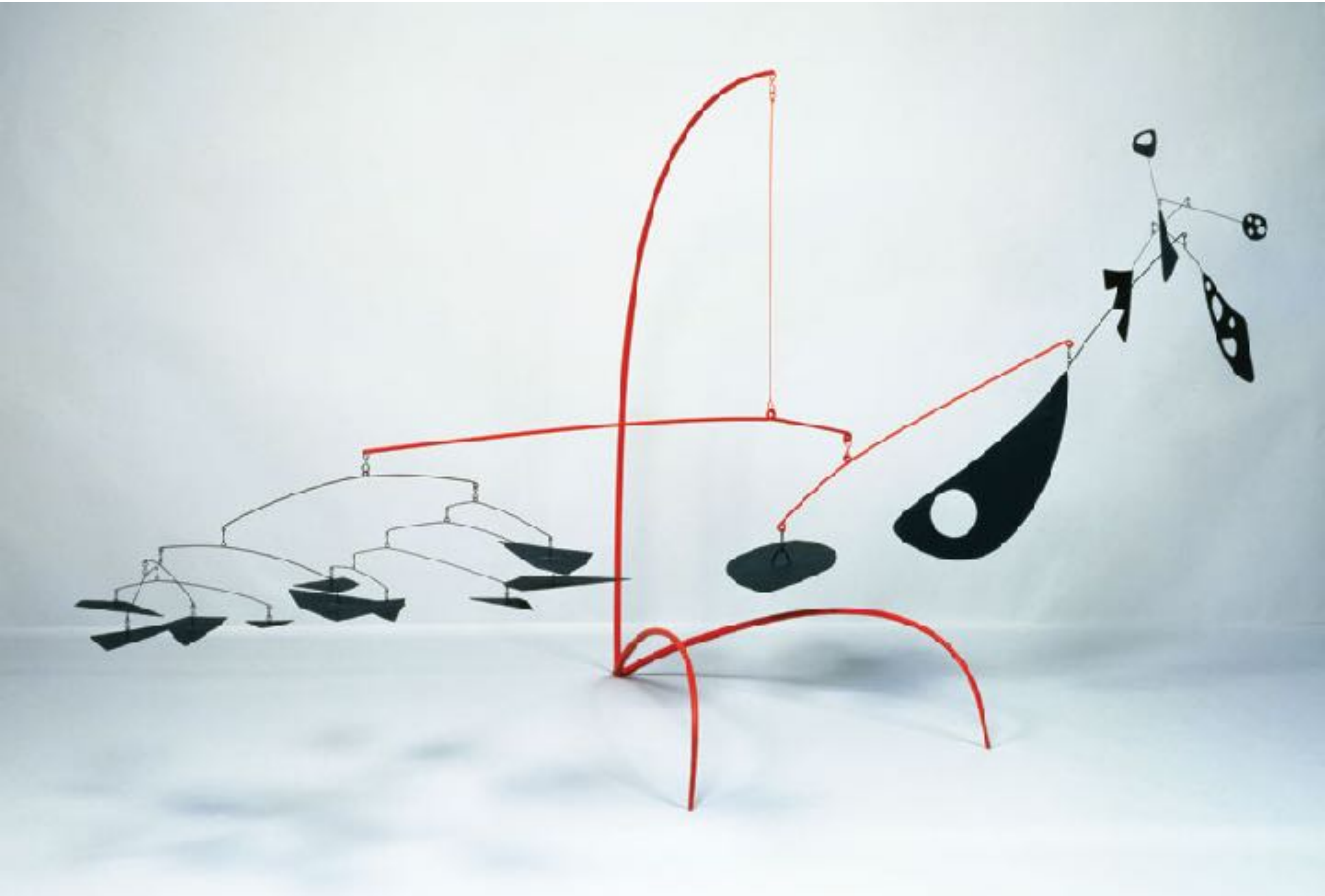
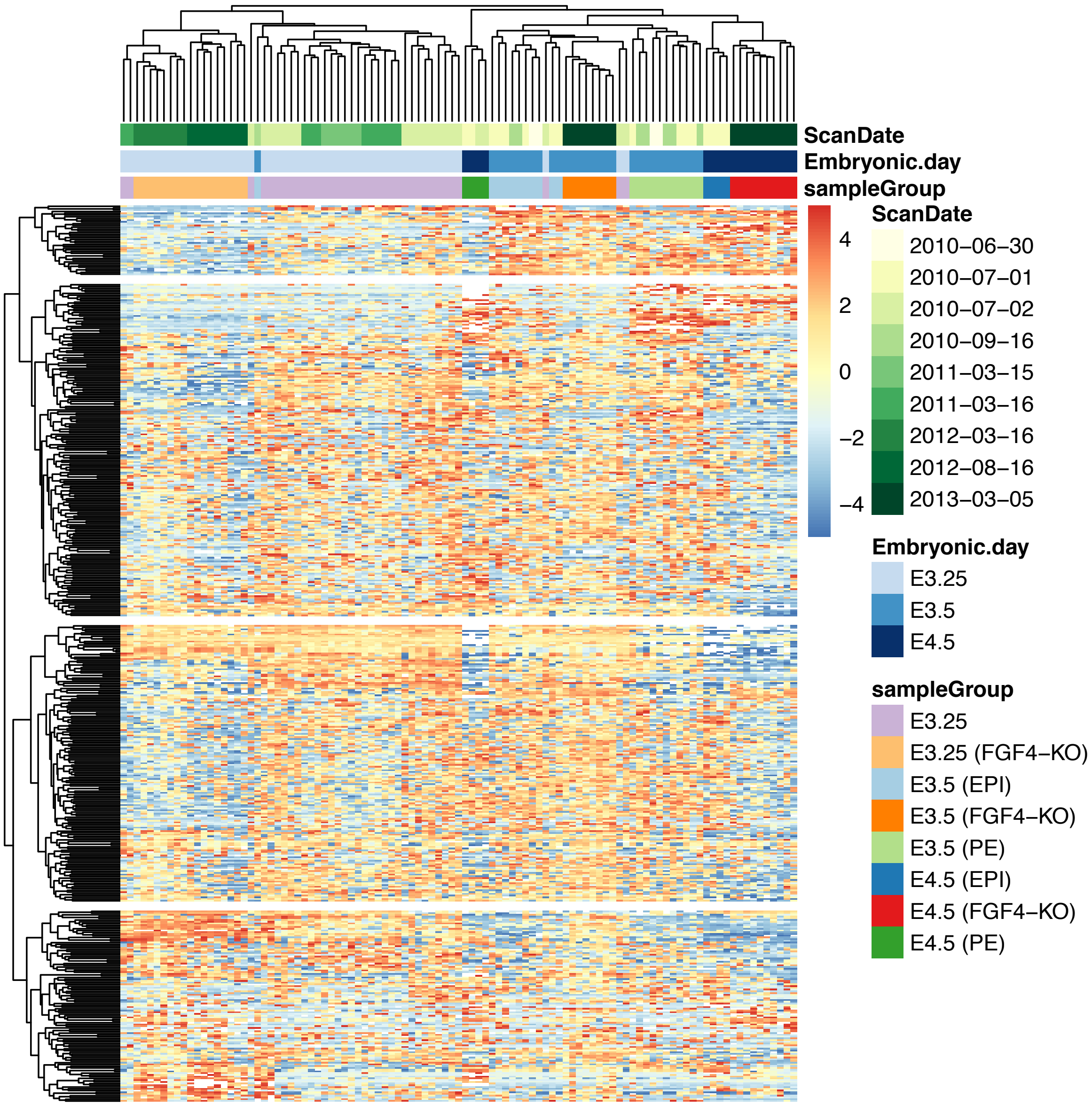
The ordering of the branches is not unique



The **order** of dendrogram **branches** is not unique



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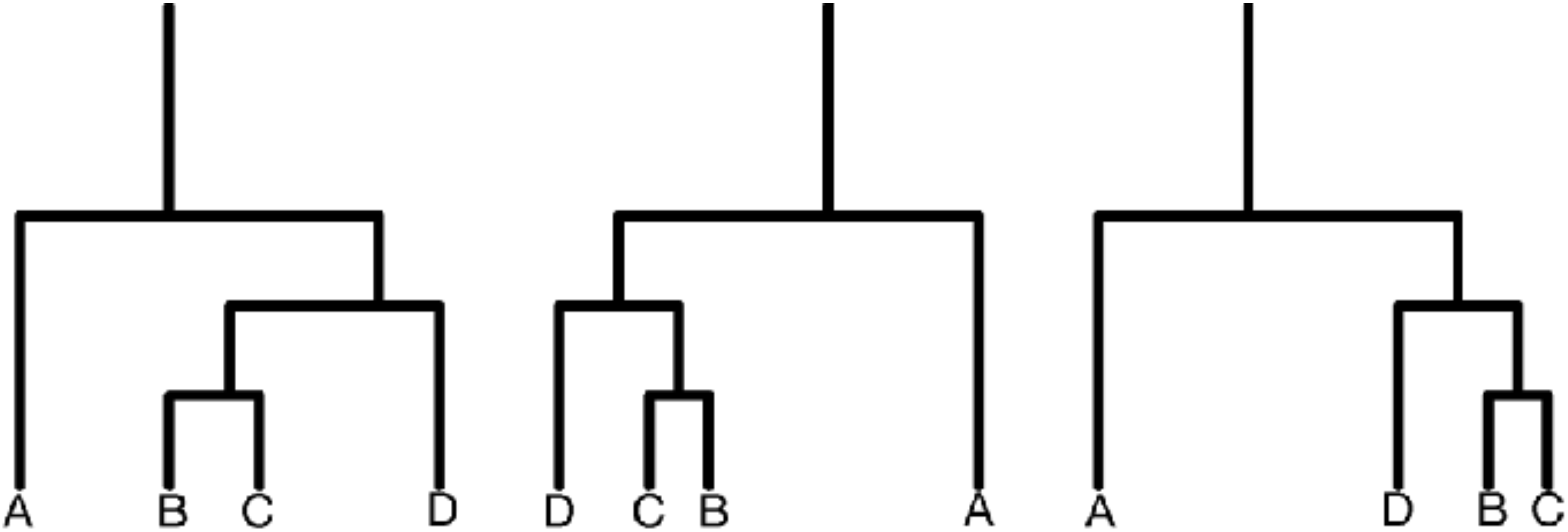
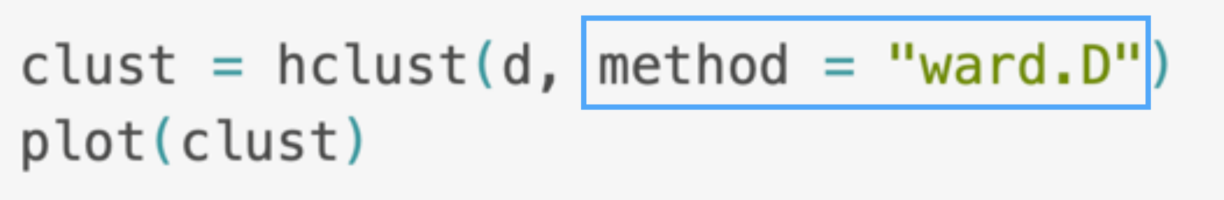
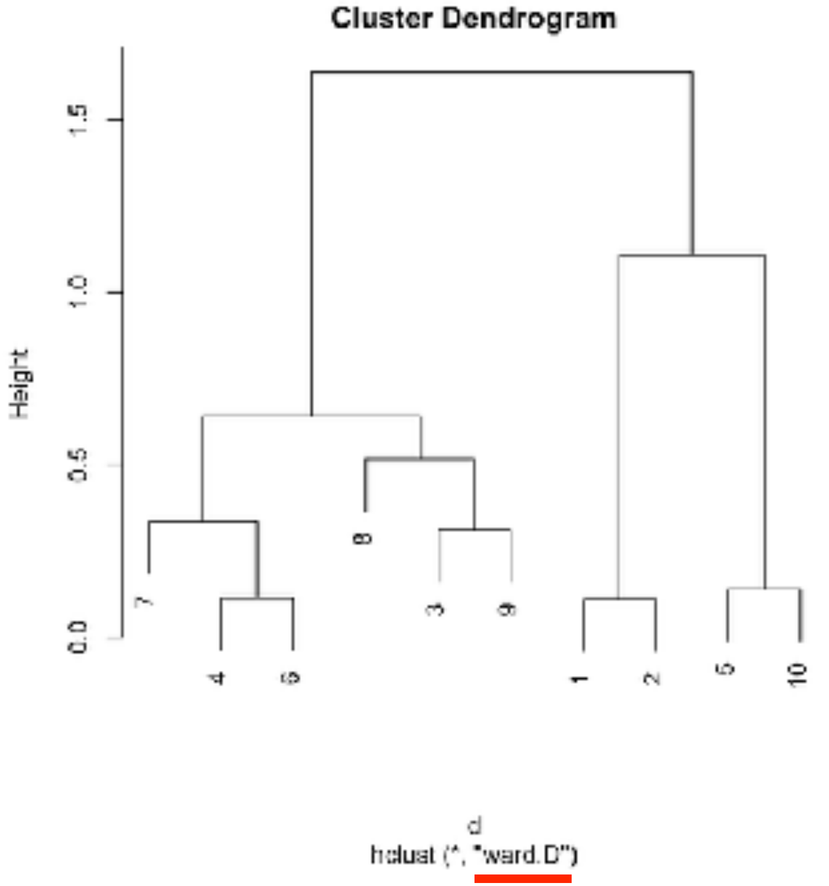


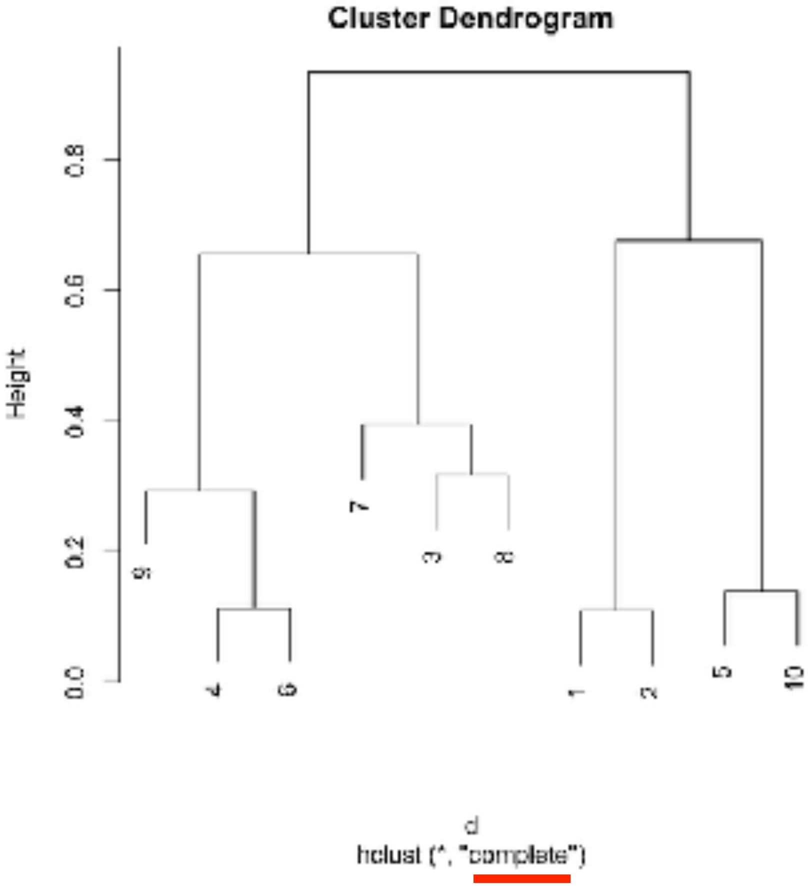
What matters is the “**order of the agglomerations**” and the **length between leaves**

Different options to agglomerate



```
clust = hclust(d, method = "ward.D")
plot(clust)
```

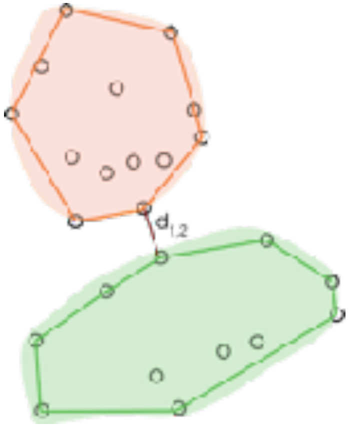




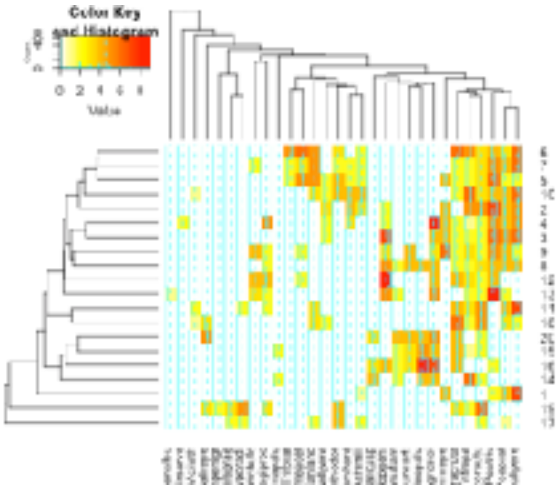
Can you think of different ways to agglomerate a new point (or subgroup) ?

Different options to agglomerate

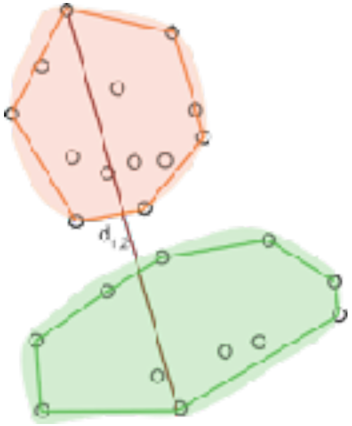
Single linkage



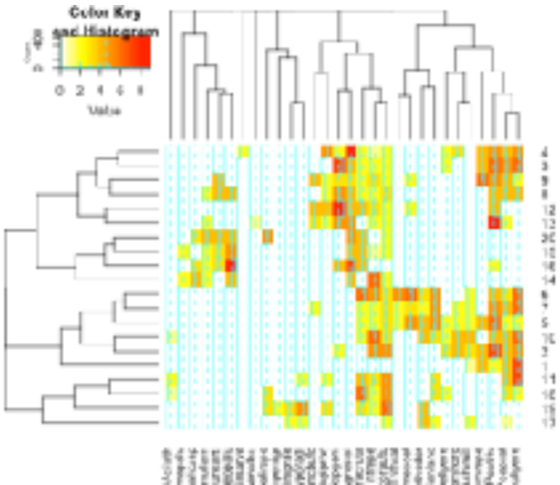
Good for recognizing the number of clusters
But “combs”



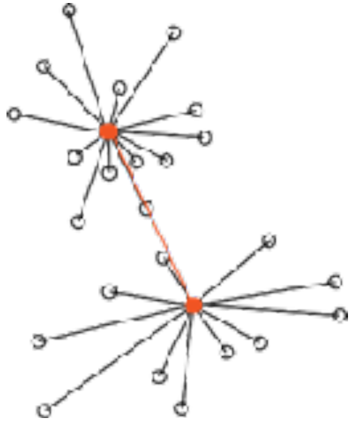
Maximal linkage



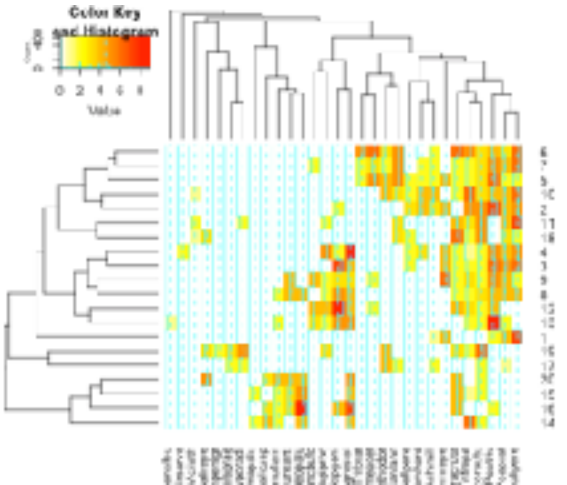
Compact classes
But one observation can alter groups



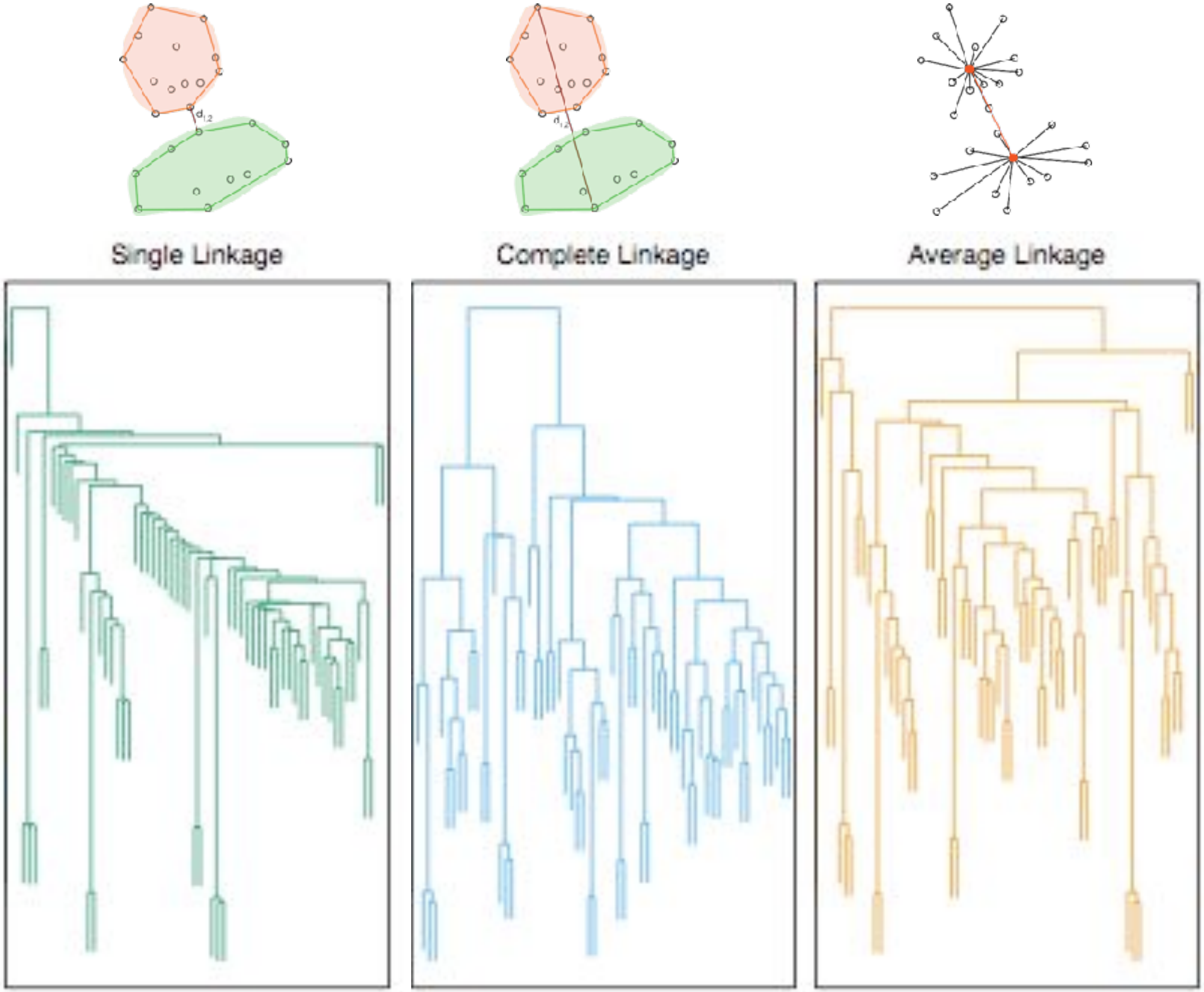
Medoids



More robust to outliers



Different options lead to **different tree shapes**



Single Linkage

Complete Linkage

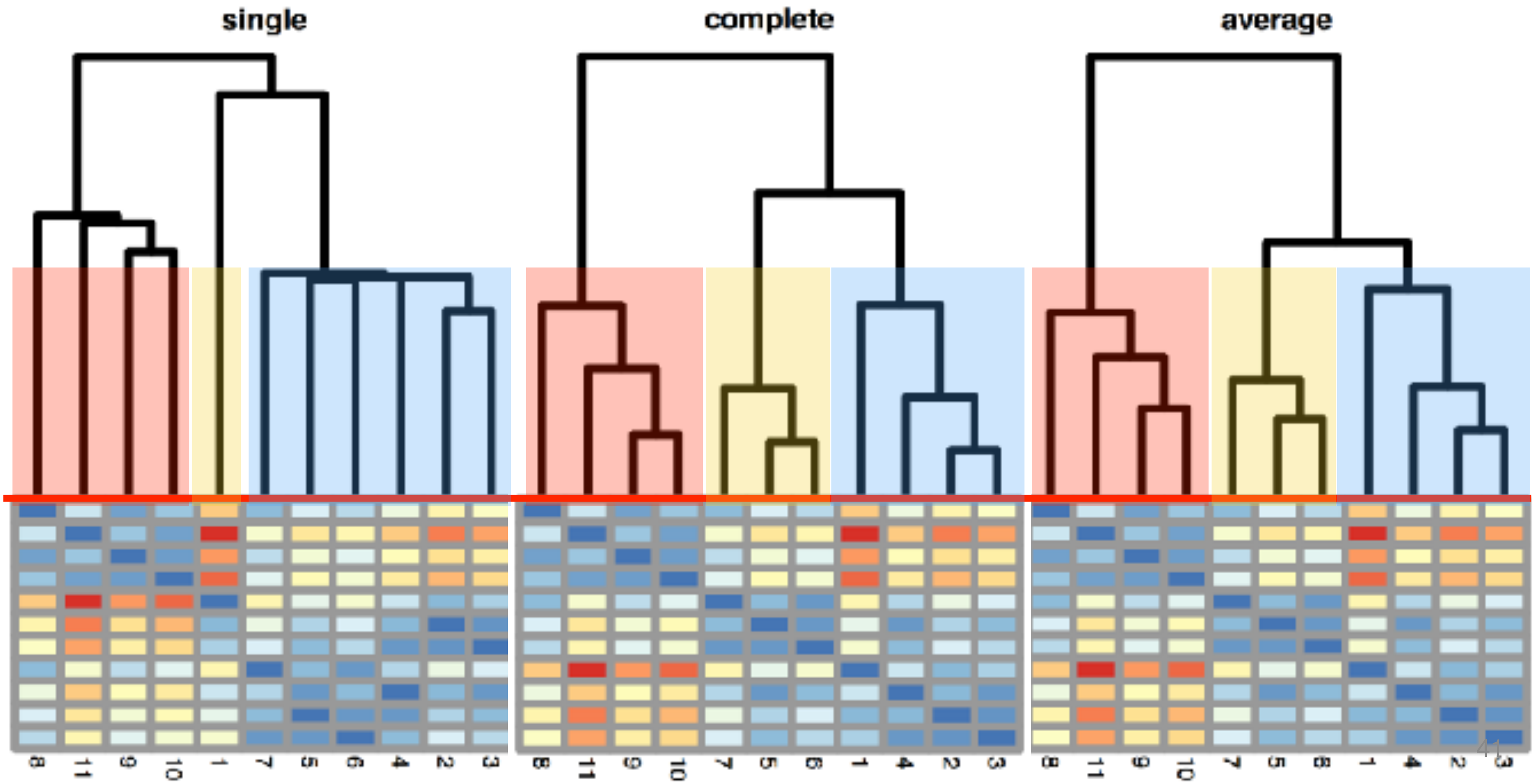
Average Linkage

# of clusters <-> max dist between groups

You cut the tree such that

- you have a given number of cluster
- at a given height (distance between the groups)

How do you choose the number of clusters?



Goals for this lecture

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Clustering methods WILL find clusters

… even if there are none

How do we validate the clusters?

How do we find the optimal number of cluster?

We want to
Minimize the distance between the points of a cluster (cohesion),
Maximizing the distance between clusters (separation).

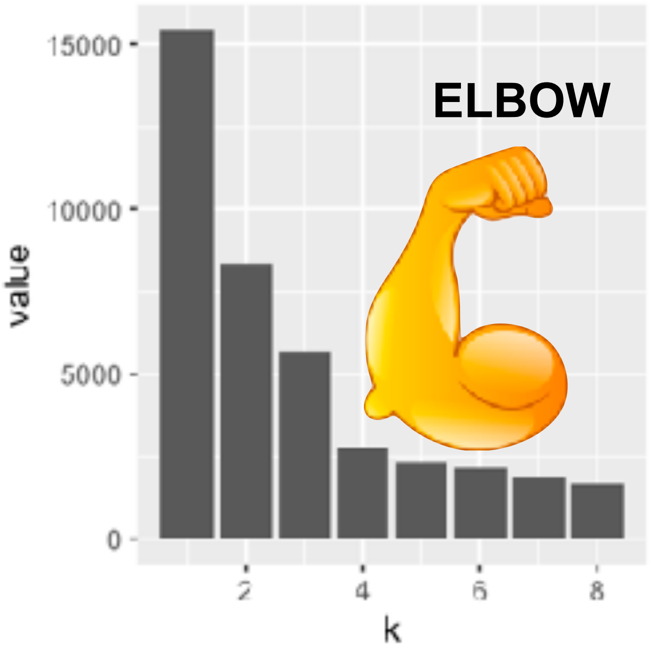
There are different ways to assess this.

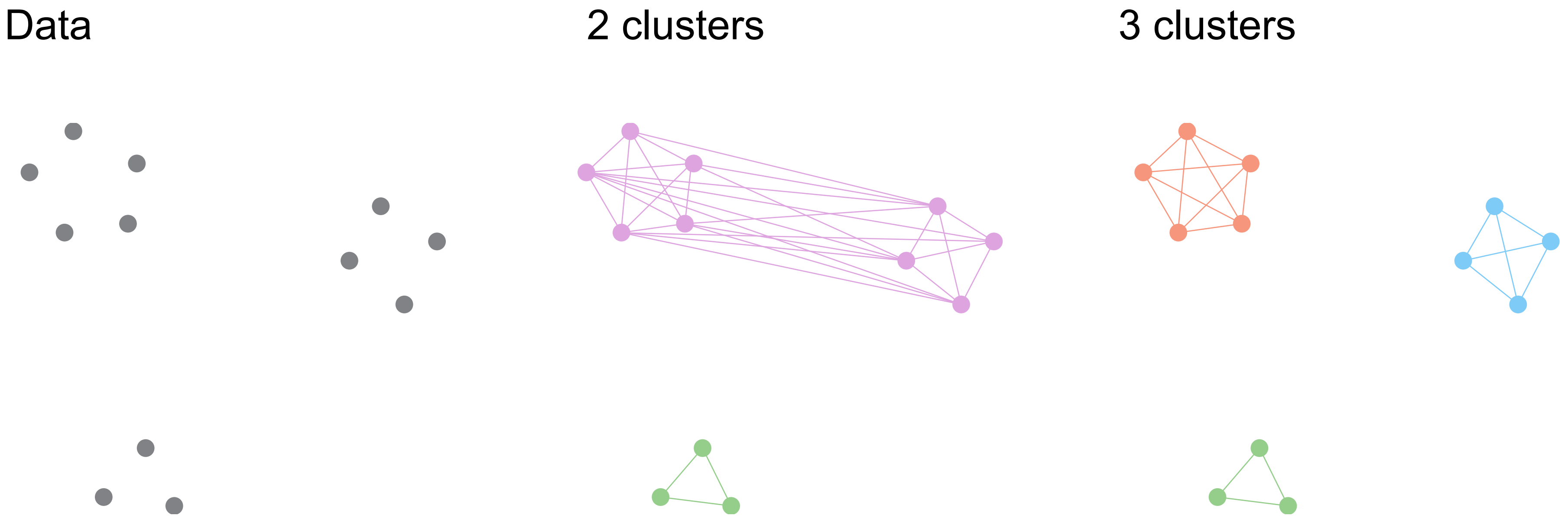
- > WSS (Within-group sum of squares)
- Elbow method
- Calinski-Harabasz index
- Gap statistic

- Silhouette method

WSS

$$\mathrm{WSS}_k = \sum_{\ell=1}^{k} \sum_{x_i \in C_\ell} d^2(x_i, \bar{x}_\ell)$$




Data

2 clusters

3 clusters

Calinski-Harabasz index

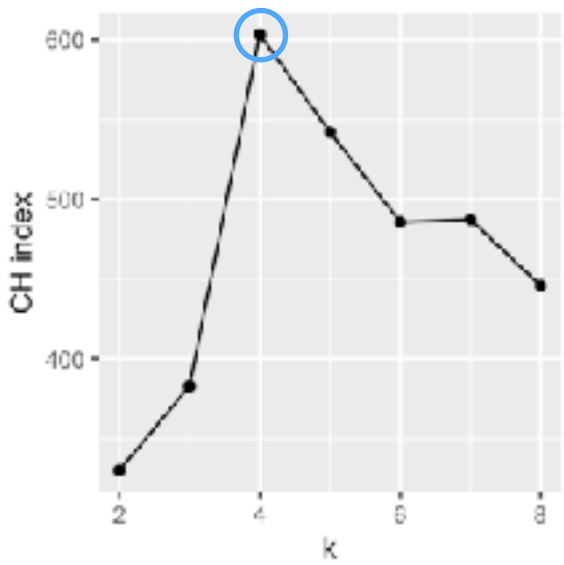
We want to maximize

$$\mathrm{CH}(k) = \frac{\text{Between-groups sum of squares}}{\text{Within-groups sum of squares}}$$

We want to maximize

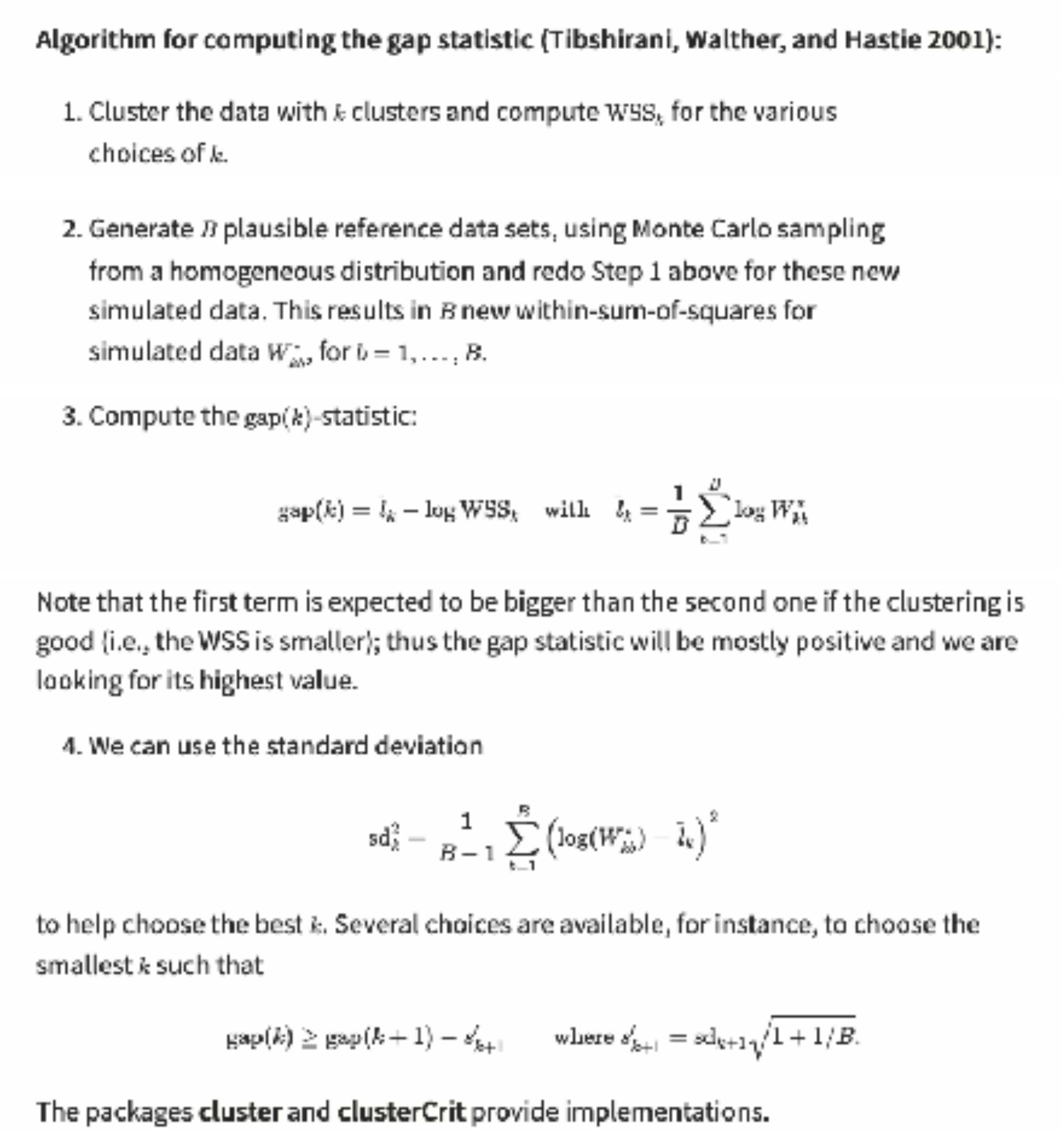
We want to minimize

$$\mathrm{CH}(k) = \frac{\mathrm{BSS}_k}{\mathrm{WSS}_k} \times \frac{N-k}{N-1} \qquad \text{where} \quad \mathrm{BSS}_k = \sum_{\ell=1}^{k} n_\ell (\bar{x}_\ell - \bar{x})^2,$$



where $\bar{x}$ is the overall center of mass (average point).

The Gap statistic



Algorithm for computing the gap statistic (Tibshirani, Walther, and Hastie 2001):

1. Cluster the data with k clusters and compute WSS_k for the various choices of k.

2. Generate B plausible reference data sets, using Monte Carlo sampling from a homogeneous distribution and redo Step 1 above for these new simulated data. This results in B new within-sum-of-squares for simulated data W^*_{kb}, for $b = 1, \ldots, B$.

3. Compute the $\text{gap}(k)$-statistic:

$$\text{gap}(k) = \bar{l}_k - \log \text{WSS}_k \quad \text{with} \quad \bar{l}_k = \frac{1}{B}\sum_{b=1}^{B} \log W^*_{kb}$$

Note that the first term is expected to be bigger than the second one if the clustering is good (i.e., the WSS is smaller); thus the gap statistic will be mostly positive and we are looking for its highest value.

4. We can use the standard deviation

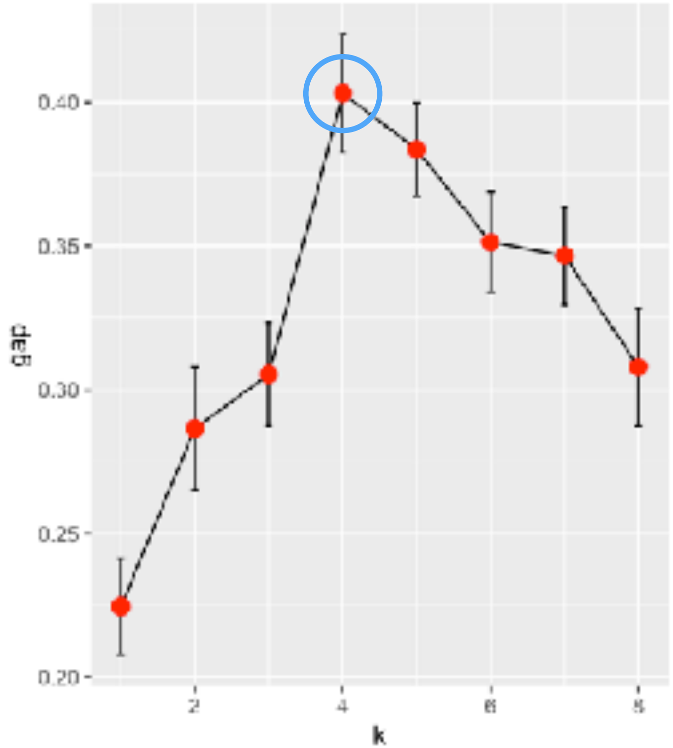
$$\text{sd}^2_k = \frac{1}{B-1}\sum_{b=1}^{B}\left(\log(W^*_{kb}) - \bar{l}_k\right)^2$$

to help choose the best k. Several choices are available, for instance, to choose the smallest k such that

$$\text{gap}(k) \geq \text{gap}(k+1) - s'_{k+1} \qquad \text{where } s'_{k+1} = \text{sd}_{k+1}\sqrt{1 + 1/B}.$$

The packages **cluster** and **clusterCrit** provide implementations.

Monte Carlo



The Silhouette method

a_i = average of —

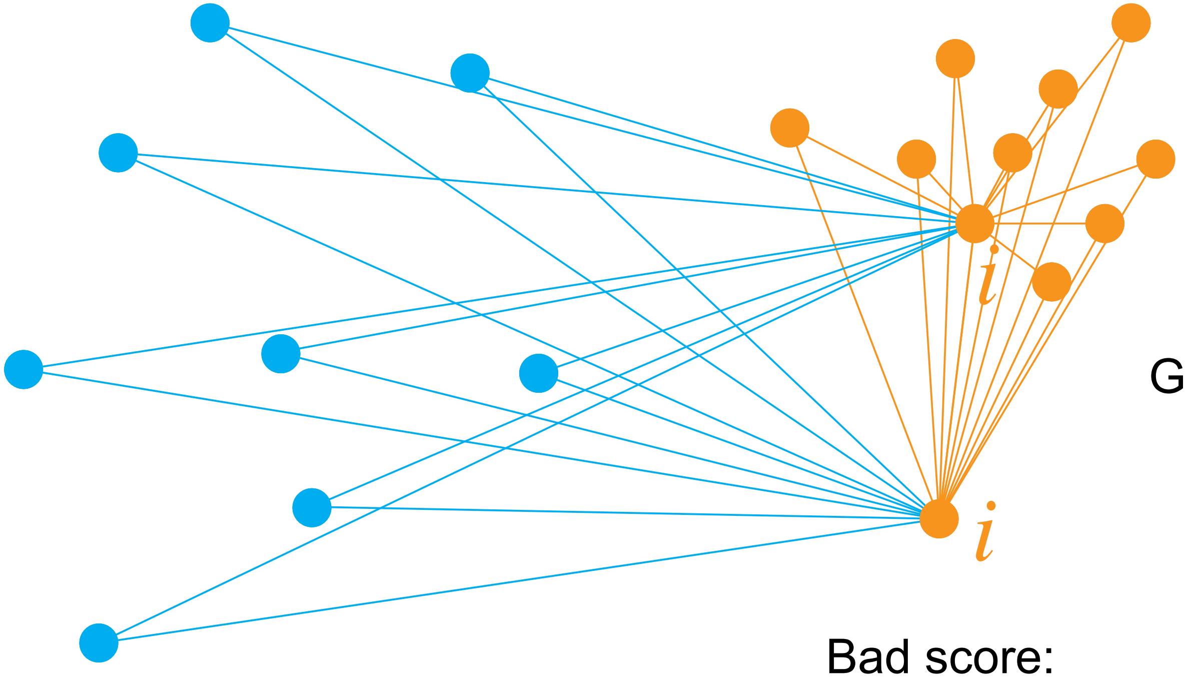
b_i = average of —

For each datapoint we compare

- the **average distance** to all the points of its **own cluster**
- the **average distance** to all the points of the **nearest cluster**

$$s_i = \frac{b_i - a_i}{max\{a_i, b_i\}}$$

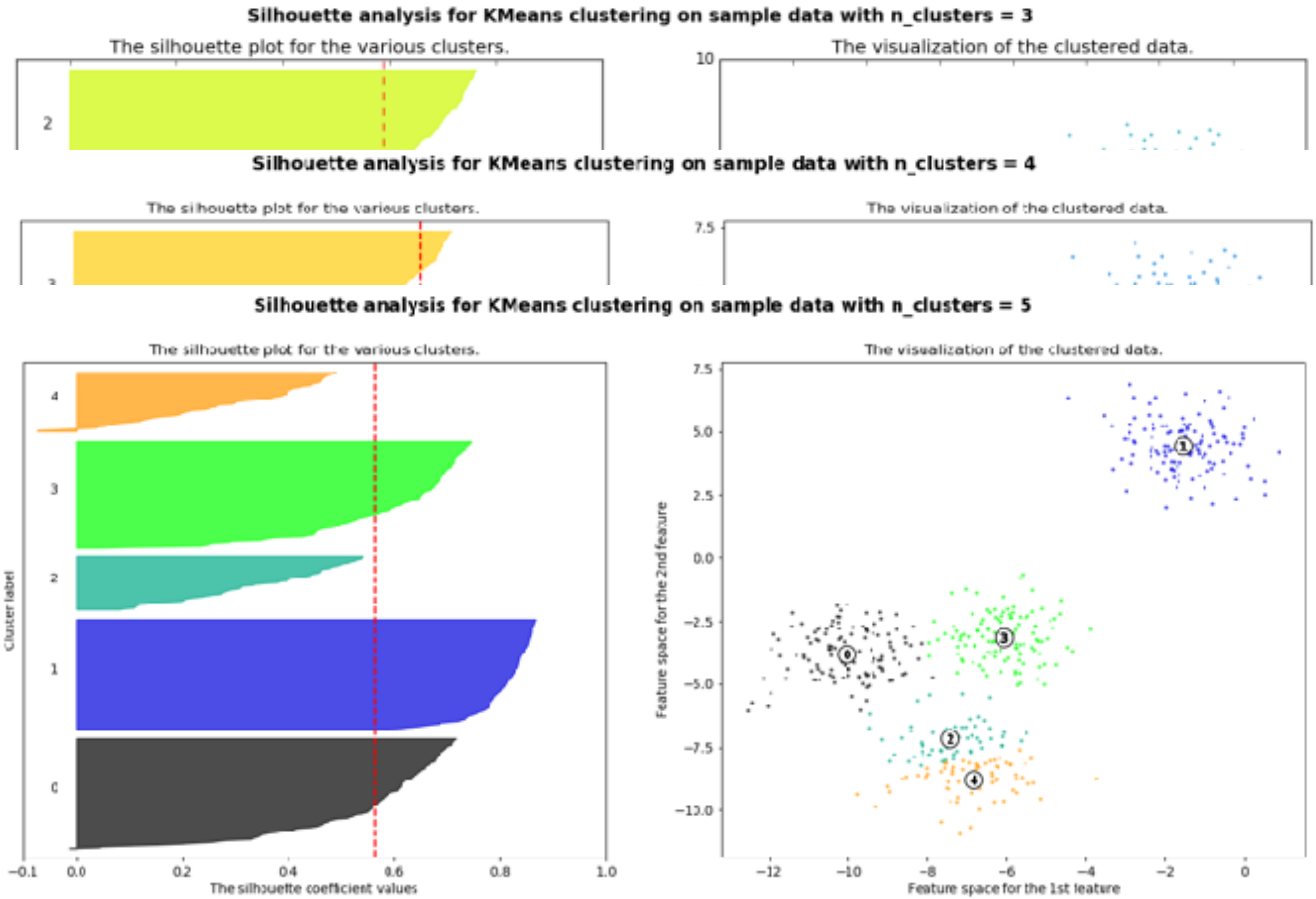
$$-1 \leq s_i \leq 1$$



Good score

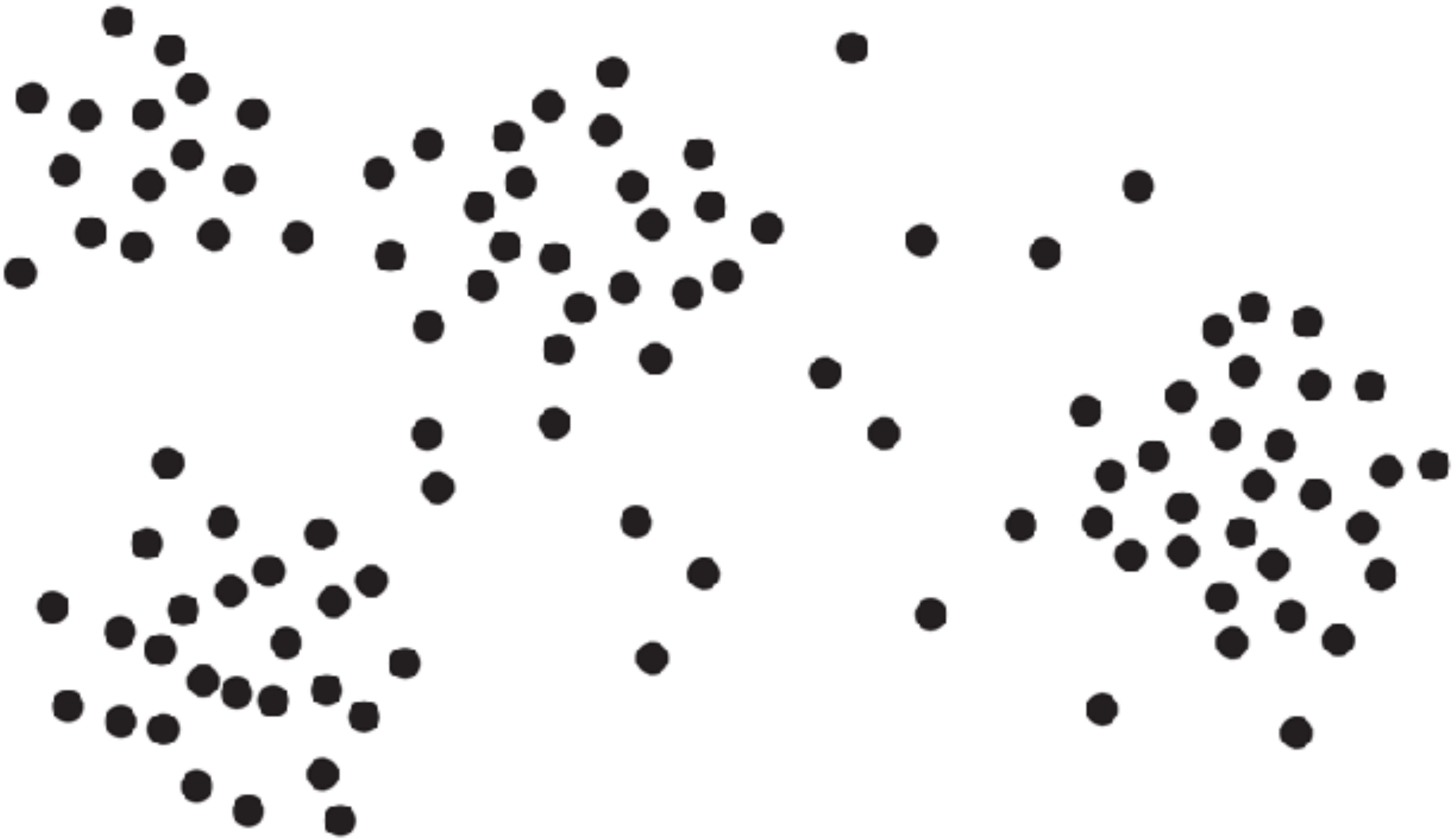
Bad score:
Not very well integrated in the cluster

The Silhouette method



The bootstrap to validate clusters

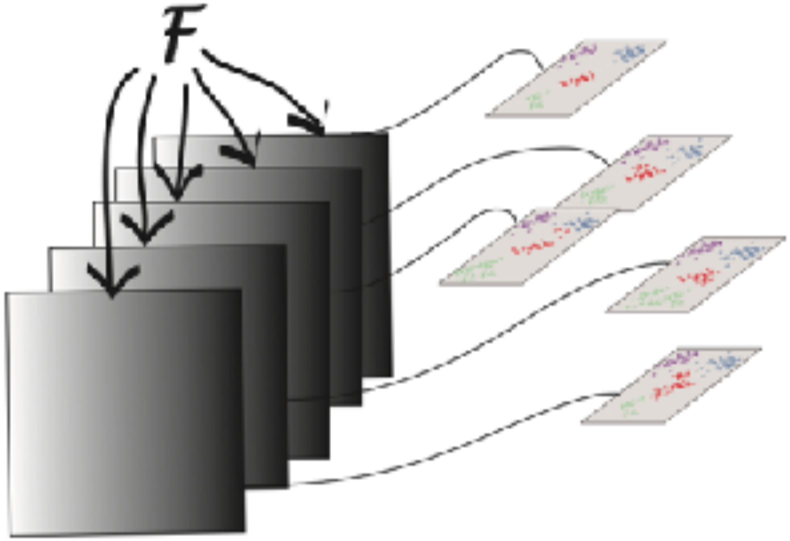
How do we apply the bootstrap?

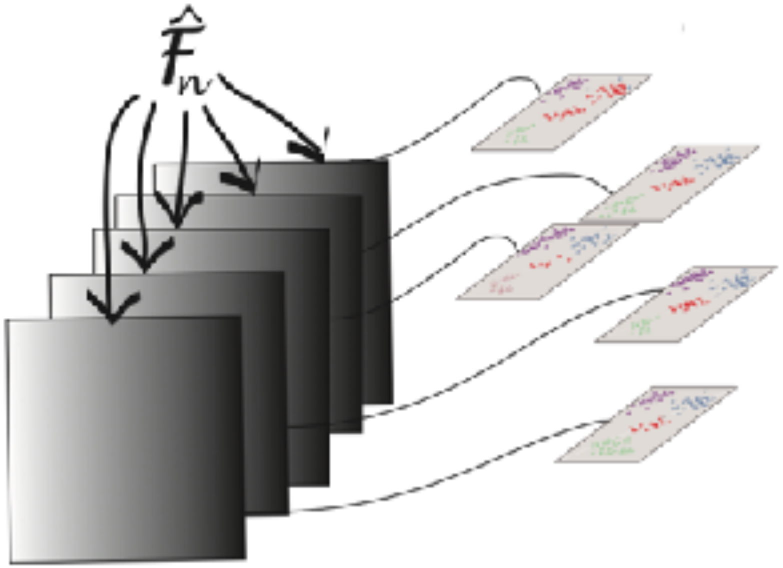


We create new datasets by subsampling the original dataset and evaluate how clusters are conserved.

Bootstrap for Clustering methods

Monte Carlo





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Some extra notes

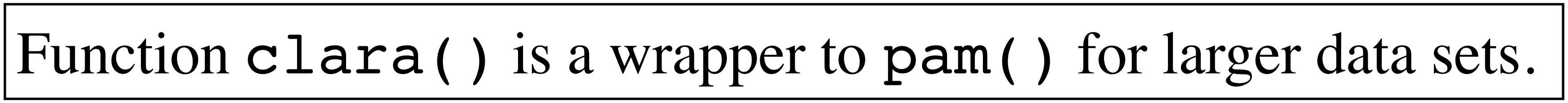
No need to invent your own clustering

There are already too many!

https://cran.r-project.org/web/views/Cluster.html

If you have VERY large datasets

Computing the distance between each pair of datapoint is NOT reasonable



Function `clara()` is a wrapper to `pam()` for larger data sets.

Partitioning method (k-medoids)

It uses **subsamples** of the original dataset,
looks for **conserved clusters**,
Finds their **medoids**,
Compute the **distance of the remaining data points** to the medoids,
Attribute a cluster to each datapoint.

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2. Explain **non-parametric methods** such as ***k-means*** or ***k-medoids***

   (also mentioned density based clustering: however cursed)

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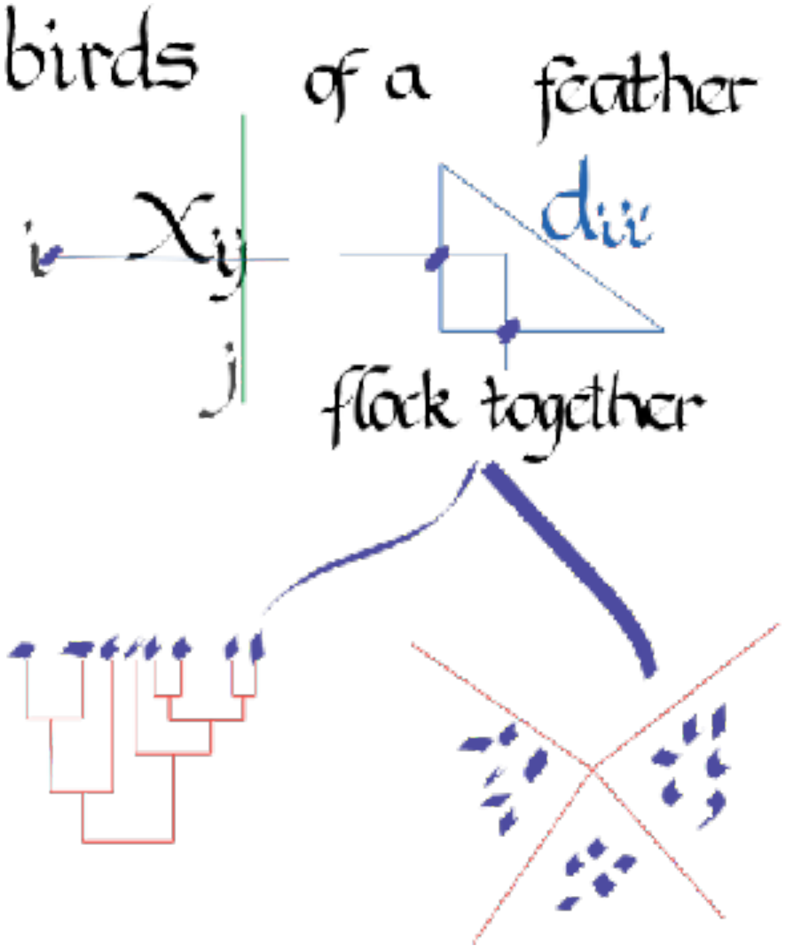
Summary

Summary: the clustering workflow



1. Start with the data.
   What are the **measurements**?
   What **type** of data?

2. Define or select a **metric (distance)** to evaluate the (dis)similarity between 2 samples.

3. Choose a **clustering method**: bottom-up (*hierarchical*) or top-down (*k-methods*)

4. **Validate** the clustering and evaluate the **optimal number** of clusters

5. **Augment** your data with the cluster information

Distances

We saw at the start of the Lecture how finding the **right** distance is an essential first step in a clustering analysis. This is a case when the ***garbage in, garbage out*** motto is in full force. Always choose a distance which is **scientifically meaningful** and compare output from as many distances as possible. Sometimes the same data require **different distances** when **different scientific objectives** are pursued.

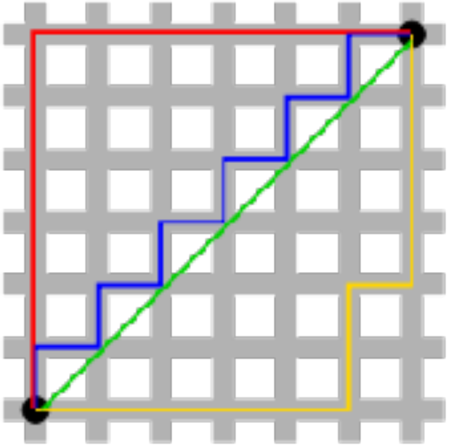
Partitioning and Aggregating

We saw two different types of clustering approaches:
iterative partitioning approaches such as kmeans and kmedoids (PAM) that alternated between estimating the clusters and assigning points to them and **hierarchical clustering** approaches that agglomerate points and then small clusters into larger ones in a nested sequence of sets that can be represented by hierarchical clustering trees.

Cluster validation

Clustering algorithms ***always*** deliver clusters so we need to assess their quality and the number of clusters to choose carefully.
These validation steps are done using visualization tools and repeating the clustering on many resamples of the data. We saw how statistics such as the bss/wss or log(wss) can be calibrated using simulation on data where we understand the group structure and can provides useful benchmarks for choosing the number of cluster.

The choice or definition of **distance depends on the data**



Euclidean distance (L2) $d(A,B)=\sqrt{(a_1-b_1)^2+(a_2-b_2)^2+\ldots+(a_p-b_p)^2}.$

Manhattan distance (L1) $d(A,B)=|a_1-b_1|+|a_2-b_2|+\ldots+|a_p-b_p|.$

Maximum distance (L∞) $d_\infty(A,B)=\max_i|a_i-b_i|.$

Minkowski distance (L*m*) $d(A,B)=((a_1-b_1)^m+(a_2-b_2)^m+\ldots+(a_p-b_p)^m)^{\frac{1}{m}}.$

Edit (Hamming) distance

Binary distance

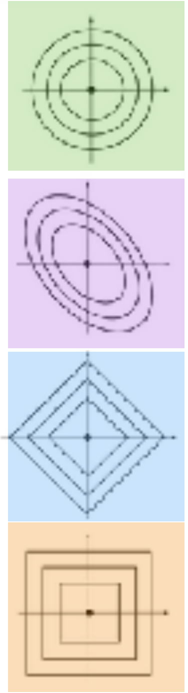
Jaccard distance $d_J(S,T)=1-J(S,T)=\dfrac{f_{01}+f_{10}}{f_{01}+f_{10}+f_{11}}.$

Correlation-based distance $d(A,B)=\sqrt{2(1-\mathrm{cor}(A,B))}.$

Weighted Euclidean distance

Mahalanobis distance

…



Questions

?

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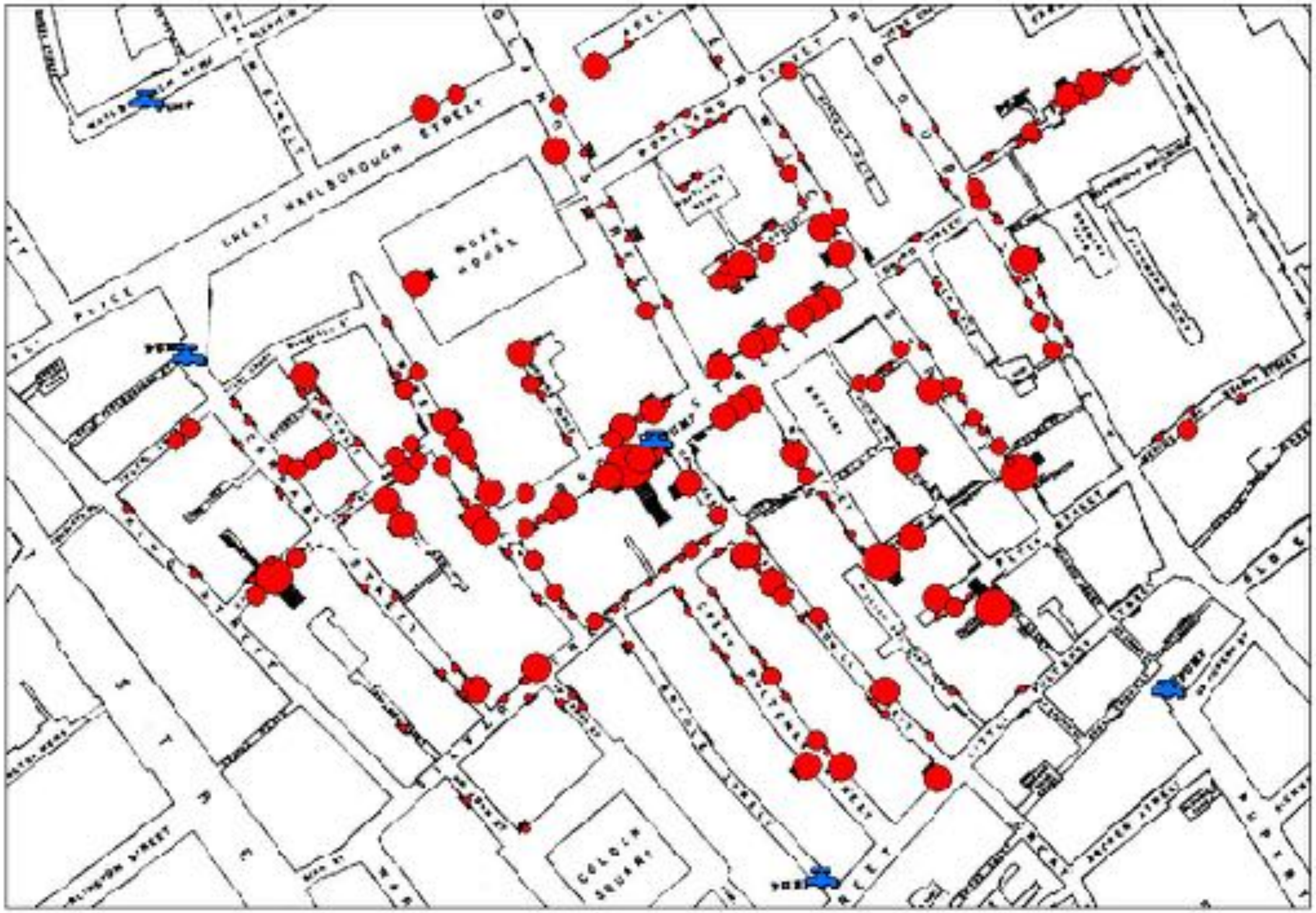
4. Understand how to **validate the clusters** and select the **optimal number of clusters**.

5. Examples in R - lab is important.

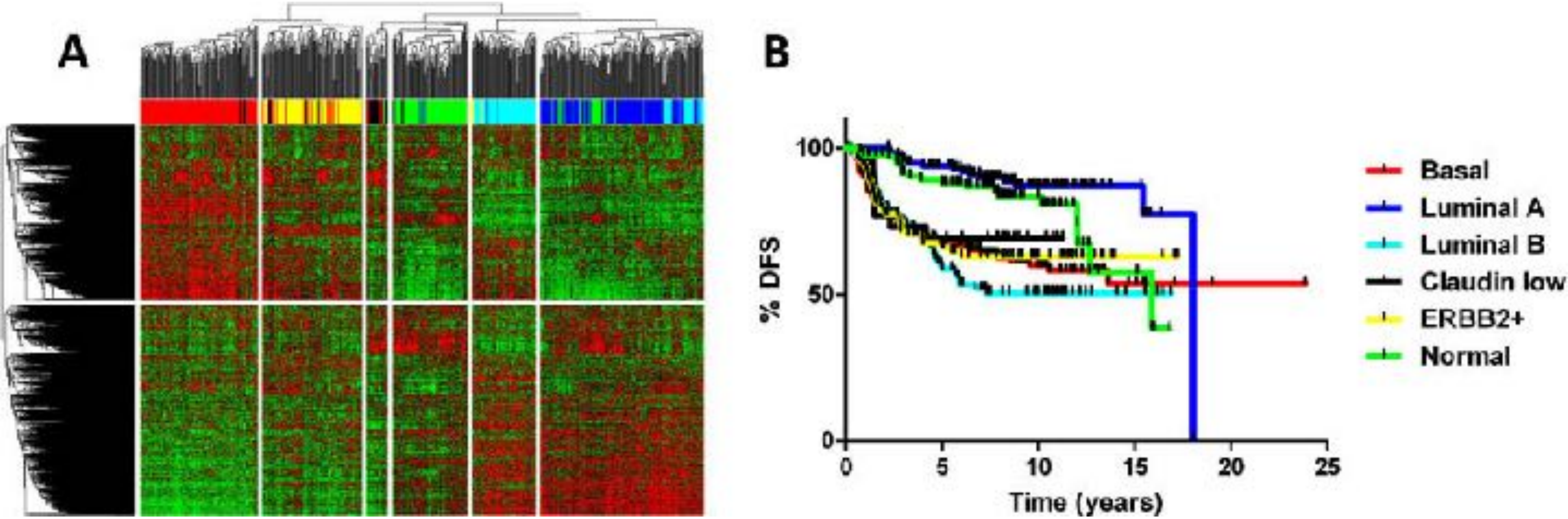
6. Why do we cluster ?

Why do we cluster ?

- **Hidden variables:**



Why do we cluster ?



Why do we cluster ?

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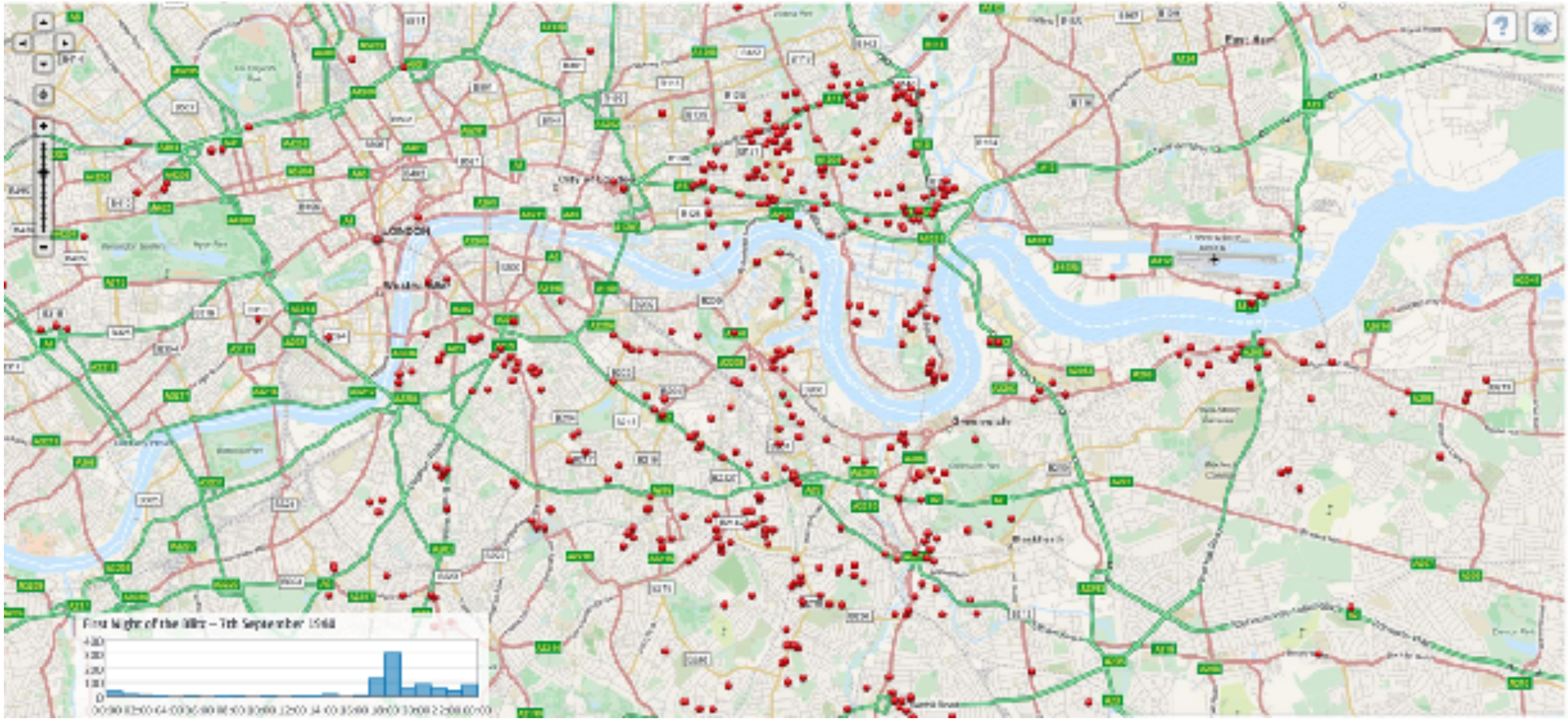

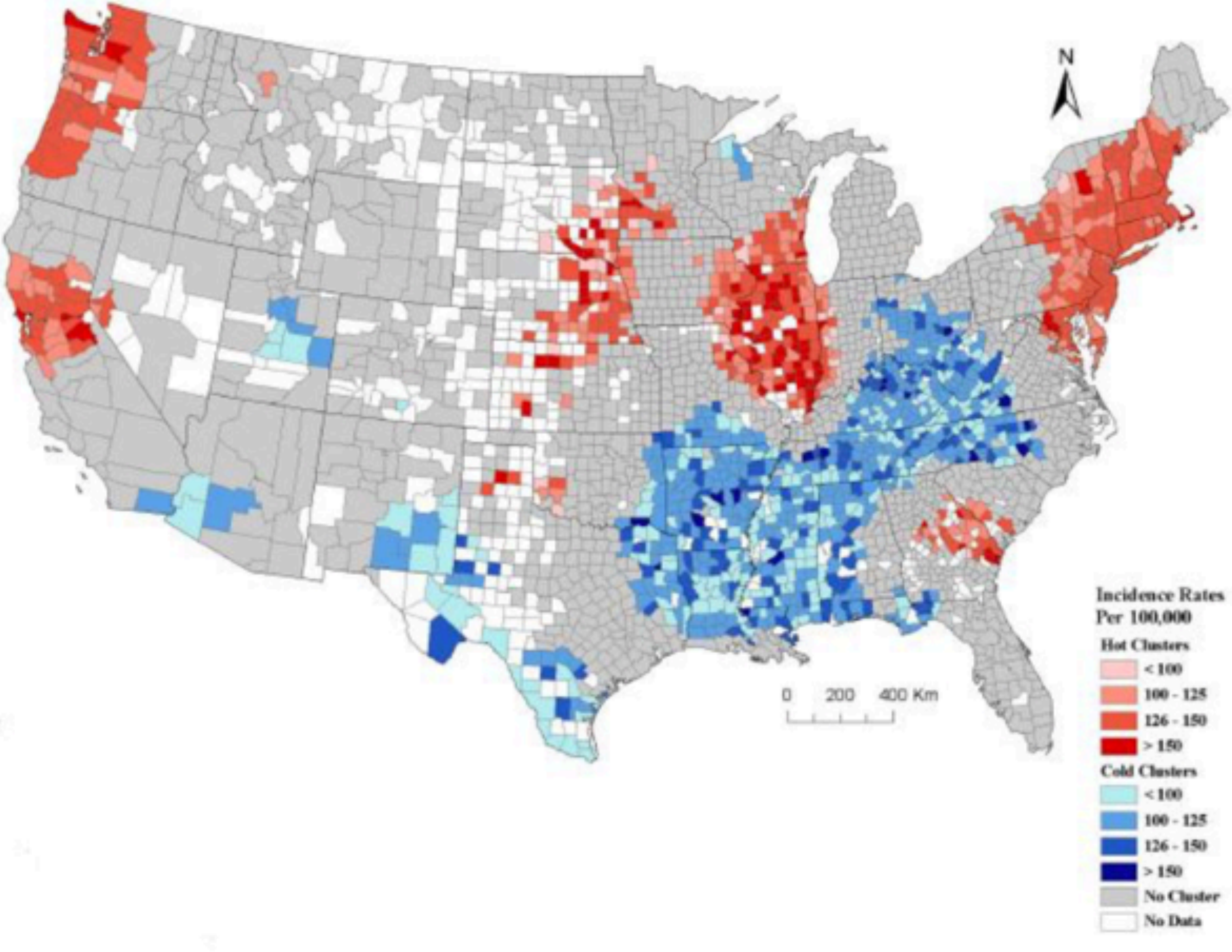
N
0 200 400 Km
Incidence Rates
Per 100,000
Hot Clusters
< 100
100 - 125
126 - 150
> 150
Cold Clusters
< 100
100 - 125
126 - 150
> 150
No Cluster
No Data