Unsupervised Learning: Clustering

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MED3007
Statistical Principles in Genomics: an Introduction with Rstudio
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1. Introduction
    - Motivation
    - Notions of similarity
2. Hierarchical Clustering Algorithms
    - Main ideas
    - Illustrative example
    - Visualization
    - Summary
3. Partitioning clustering: *k*-means
    - Partitioning Clustering Algorithms
    - Main idea of the *k*-means
    - Illustrative example 1
    - Illustrative example 2
4. Summary

Recap from last time. . .

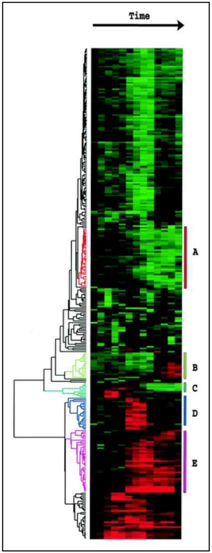
Unsupervised methods

Methods that do not make use of external information: groups / class assignments, clinical outcomes, covariates.
Aim: finding hidden structure in the data

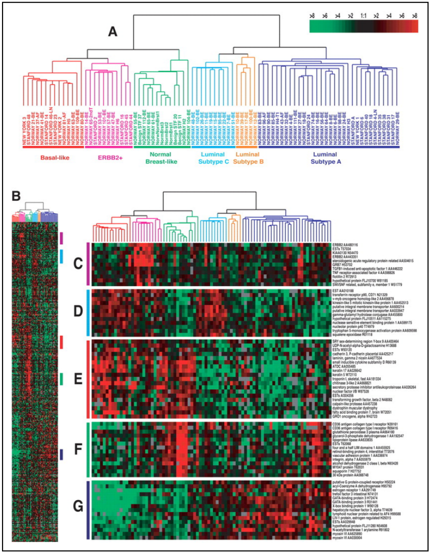
How can we find and/or visualise structure?

- Reducing dimensionality by removing noise and "uninteresting" stuff
  → TODAY – Lecture 2
- Ordering and grouping together via clustering
  → TOMORROW – Lecture 3

Heatmaps are everywhere...



Eisen et al. (1998), Figure 1



Sorlie et al. (2001), Figure 1

What is clustering?

Clustering methods

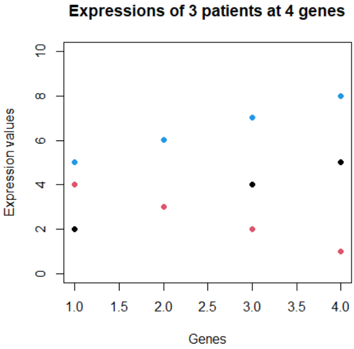
Methods that **aim at grouping** a collection of objects into groups, or clusters, such that objects within each cluster are more closely related to one another than objects assigned to a different cluster

- Distance measure
  A notion of distance or similarity of two objects: When are two objects close to each other?
- Clustering algorithm
  A procedure to minimise distances of objects within groups and/or maximise distances between groups.

What is meant when two patients are said to be “similar”?

Possibilities:

- Red and black patients are similar: **They lie close to each other.**
- Blue and black patients are similar: **They are positively correlated.**
- Red and blue patients are associated: **They are negatively correlated.**



Examples of distance measures $d(\cdot,\cdot)$

- Euclidean distance

$$d_{euc}(\mathbf{x},\mathbf{y}) = \left(\sum_{k=1}^{m}(x_k - y_k)^2\right)^{1/2}$$

- 1 - Pearson's correlation

$$d_{cor}(\mathbf{x},\mathbf{y}) = 1 - r(\mathbf{x},\mathbf{y}) = 1 - \frac{\sum_{i=1}^{m}(x_i - \bar{x})(y_i - \bar{y})}{\sqrt{\sum_{i=1}^{m}(x_i - \bar{x})^2 \sum_{i=1}^{m}(y_i - \bar{y})^2}}$$

- 1 - Spearman's rank correlation ($R(x_i)$= Rank of x_i)

$$\begin{aligned} d_{spear}(\mathbf{x},\mathbf{y}) &= 1 - r_s(\mathbf{x},\mathbf{y}) \\ &= 1 - \frac{\sum_{i=1}^{m}(R(x_i) - \overline{R(x)})(R(y_i) - \overline{R(y)})}{\sqrt{\sum_{i=1}^{m}(R(x_i) - \overline{R(x)})^2 \sum_{i=1}^{m}(R(y_i) - \overline{R(y)})^2}} \end{aligned}$$

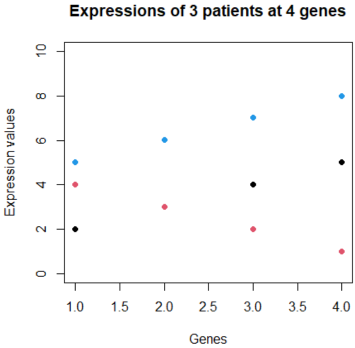
Examples of distance measures $d(\cdot,\cdot)$ – visual!

Euclidean distance:

- d(black, red) = 4.90
- d(black, blue) = 6.00
- d(blue, red) = 9.16

Spearman-correlation-distance:

- d(black, red) = 2.00
- d(black, blue) = 0.00
- d(blue, red) = 2.00



Interpretation:

- the smaller the distance, the more similar the patients' response
- different distances measure "similarity" differently

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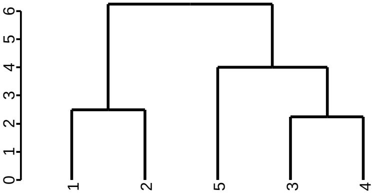
Hierarchical clustering - Agglomerative algorithm



dendrogram

- Bottom-up algorithm (top-down methods are less common)
- Start with each object assigned to its own cluster.
- In each iteration, merge the two clusters with the minimal distance from each other - until you are left with a single cluster containing all objects
- But how define the distance between two clusters?

Hierarchical clustering - Linkage

Calculation of distance d(G,H) between clusters G and H is based on pairwise distances between objects from the two clusters:

- Single linkage uses the smallest distance between the objects:

  $$d_S(G,H) = min_{(i \in G; j \in H)} d_{ij}$$

  Single linkage is not commonly used.

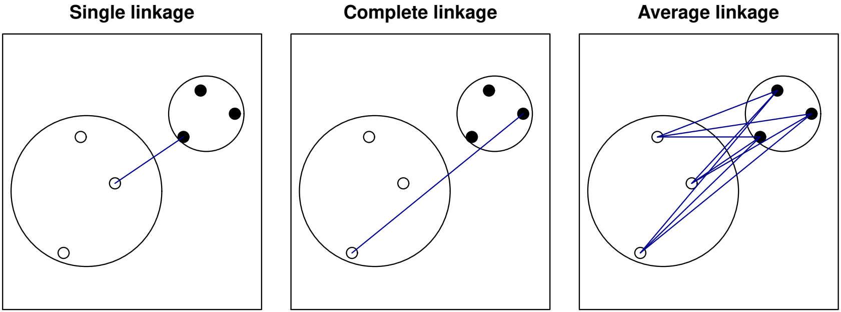
- Complete linkage uses the largest distance between the objects:

  $$d_C(G,H) = max_{(i \in G; j \in H)} d_{ij}$$

- Average linkage uses the average distance between the objects:

  $$d_A(G,H) = \frac{1}{N_G N_H} \sum_{i \in G} \sum_{j \in H} d_{ij}$$

Hierarchical clustering - Linkage illustration



Hierarchical clustering - Single linkage example

- Data: 5 patients 1-5 (= rows), 2 expression arrays A,B (= columns)
- Method: **Agglomerative hierarchical clustering** using **Single-Linkage**

Expression matrix

$$\left(\begin{array}{ccc} & A & B \\ 1 & 5.0 & 7.0 \\ 2 & 5.5 & 8.5 \\ 3 & 8.0 & 8.5 \\ 4 & 8.0 & 7.0 \\ 5 & 8.0 & 5.0 \end{array}\right)$$

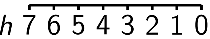
Distance matrix
(**Euclidean distance**)

$$\left(\begin{array}{cccccc} & 1 & 2 & 3 & 4 & 5 \\ 1 & 0.00 & 2.50 & 11.25 & 9.00 & 13.00 \\ 2 & 2.50 & 0.00 & 6.25 & 8.50 & 18.50 \\ 3 & 11.25 & 6.25 & 0.00 & 2.25 & 12.25 \\ 4 & 9.00 & 8.50 & 2.25 & 0.00 & 4.00 \\ 5 & 13.00 & 18.50 & 12.25 & 4.00 & 0.00 \end{array}\right)$$

Agglomerative clustering - Single linkage example

distance matrix

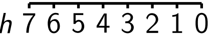
$$\begin{array}{c|c}
1 & \\
2 & \\
3 & \\
4 & \\
5 &
\end{array}
\begin{bmatrix}
0.00 & 2.50 & 11.25 & 9.00 & 13.00 \\
2.50 & 0.00 & 6.25 & 8.50 & 18.50 \\
11.25 & 6.25 & 0.00 & 2.25 & 12.25 \\
9.00 & 8.50 & 2.25 & 0.00 & 4.00 \\
13.00 & 18.50 & 12.25 & 4.00 & 0.00
\end{bmatrix}$$



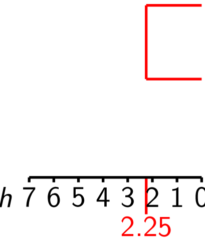
Agglomerative clustering - Single linkage example

distance matrix

$$\begin{array}{c|c}
1 & \\
2 & \\
3 & \\
4 & \\
5 & \\
\end{array}
\begin{bmatrix}
0.00 & 2.50 & 11.25 & 9.00 & 13.00 \\
2.50 & 0.00 & 6.25 & 8.50 & 18.50 \\
11.25 & 6.25 & 0.00 & \boxed{2.25} & 12.25 \\
9.00 & 8.50 & \boxed{2.25} & 0.00 & 4.00 \\
13.00 & 18.50 & 12.25 & 4.00 & 0.00
\end{bmatrix}$$



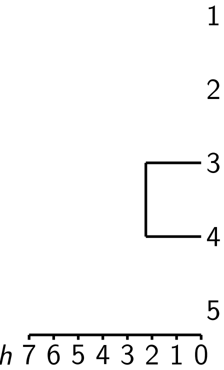
Agglomerative clustering - Single linkage example



distance matrix

$$
\begin{array}{c|c}
1 & \\
2 & \\
3 & \\
4 & \\
5 &
\end{array}
\begin{bmatrix}
0.00 & 2.50 & 11.25 & 9.00 & 13.00 \\
2.50 & 0.00 & 6.25 & 8.50 & 18.50 \\
11.25 & 6.25 & 0.00 & 2.25 & 12.25 \\
9.00 & 8.50 & 2.25 & 0.00 & 4.00 \\
13.00 & 18.50 & 12.25 & 4.00 & 0.00
\end{bmatrix}
$$

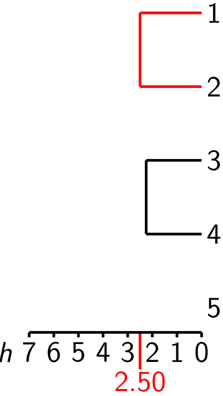
Agglomerative clustering - Single linkage example



distance matrix

$$\begin{bmatrix} 0.00 & 2.50 & 11.25 & 9.00 & 13.00 \\ 2.50 & 0.00 & 6.25 & 8.50 & 18.50 \\ 11.25 & 6.25 & 0.00 & 2.25 & 12.25 \\ 9.00 & 8.50 & 2.25 & 0.00 & 4.00 \\ 13.00 & 18.50 & 12.25 & 4.00 & 0.00 \end{bmatrix}$$

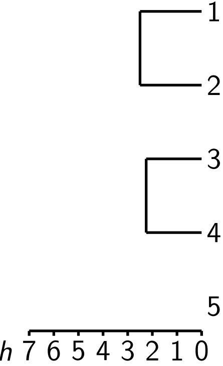
Agglomerative clustering - Single linkage example



distance matrix

$$\begin{bmatrix} 0.00 & 2.50 & 11.25 & 9.00 & 13.00 \\ 2.50 & 0.00 & 6.25 & 8.50 & 18.50 \\ 11.25 & 6.25 & 0.00 & 2.25 & 12.25 \\ 9.00 & 8.50 & 2.25 & 0.00 & 4.00 \\ 13.00 & 18.50 & 12.25 & 4.00 & 0.00 \end{bmatrix}$$

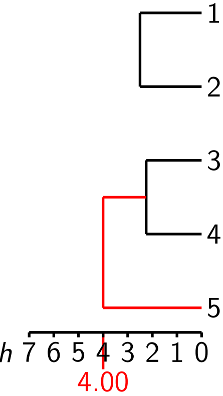
Agglomerative clustering - Single linkage example



distance matrix

$$\begin{bmatrix} 0.00 & 2.50 & 11.25 & 9.00 & 13.00 \\ 2.50 & 0.00 & 6.25 & 8.50 & 18.50 \\ 11.25 & 6.25 & 0.00 & 2.25 & 12.25 \\ 9.00 & 8.50 & 2.25 & 0.00 & 4.00 \\ 13.00 & 18.50 & 12.25 & 4.00 & 0.00 \end{bmatrix}$$

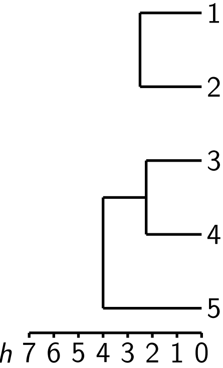
Agglomerative clustering - Single linkage example



distance matrix

$$\begin{bmatrix} 0.00 & 2.50 & 11.25 & 9.00 & 13.00 \\ 2.50 & 0.00 & 6.25 & 8.50 & 18.50 \\ 11.25 & 6.25 & 0.00 & 2.25 & 12.25 \\ 9.00 & 8.50 & 2.25 & 0.00 & 4.00 \\ 13.00 & 18.50 & 12.25 & 4.00 & 0.00 \end{bmatrix}$$

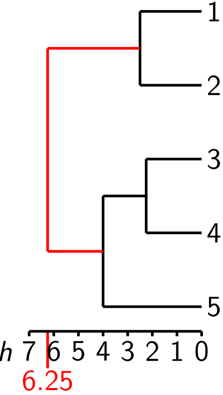
Agglomerative clustering - Single linkage example



distance matrix

$$\begin{bmatrix} 0.00 & 2.50 & 11.25 & 9.00 & 13.00 \\ 2.50 & 0.00 & 6.25 & 8.50 & 18.50 \\ 11.25 & 6.25 & 0.00 & 2.25 & 12.25 \\ 9.00 & 8.50 & 2.25 & 0.00 & 4.00 \\ 13.00 & 18.50 & 12.25 & 4.00 & 0.00 \end{bmatrix}$$

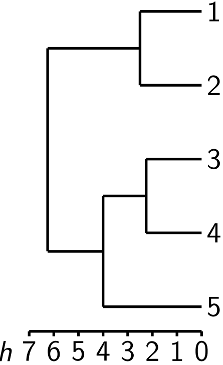
Agglomerative clustering - Single linkage example



distance matrix

$$\begin{bmatrix} 0.00 & 2.50 & 11.25 & 9.00 & 13.00 \\ 2.50 & 0.00 & 6.25 & 8.50 & 18.50 \\ 11.25 & 6.25 & 0.00 & 2.25 & 12.25 \\ 9.00 & 8.50 & 2.25 & 0.00 & 4.00 \\ 13.00 & 18.50 & 12.25 & 4.00 & 0.00 \end{bmatrix}$$

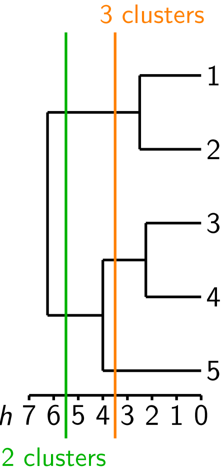
Agglomerative clustering - Single linkage example



distance matrix

$$\begin{bmatrix} 0.00 & 2.50 & 11.25 & 9.00 & 13.00 \\ 2.50 & 0.00 & 6.25 & 8.50 & 18.50 \\ 11.25 & 6.25 & 0.00 & 2.25 & 12.25 \\ 9.00 & 8.50 & 2.25 & 0.00 & 4.00 \\ 13.00 & 18.50 & 12.25 & 4.00 & 0.00 \end{bmatrix}$$

Agglomerative clustering - Single linkage example

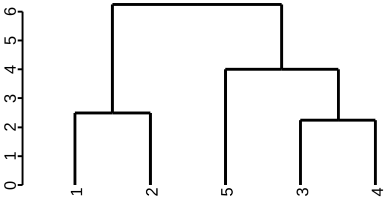


distance matrix

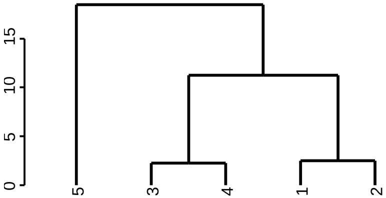
$$\begin{bmatrix} 0.00 & 2.50 & 11.25 & 9.00 & 13.00 \\ 2.50 & 0.00 & 6.25 & 8.50 & 18.50 \\ 11.25 & 6.25 & 0.00 & 2.25 & 12.25 \\ 9.00 & 8.50 & 2.25 & 0.00 & 4.00 \\ 13.00 & 18.50 & 12.25 & 4.00 & 0.00 \end{bmatrix}$$

Hierarchical clustering - Linkage methods

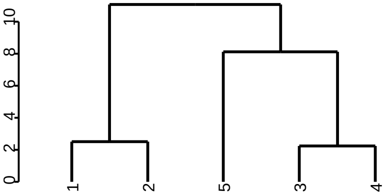
Same distance matrix!



Single Linkage

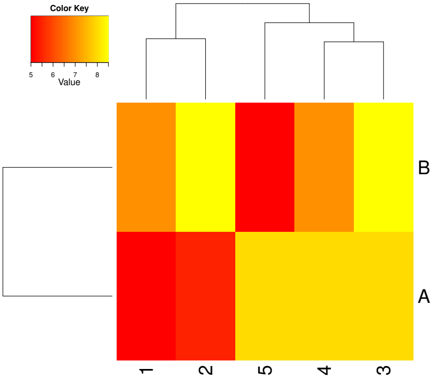


Complete Linkage



Average Linkage

Hierarchical clustering - Heatmap



- Single linkage
- Euclidean distance
- The expression values are represented as colours.

Summary & Take-home messages

- The procedure provides a hierarchy of the clustering, with the number of clusters ranging from 1 to the number of objects
- Finding a meaningful cut is similar to the problem of finding the number of clusters *k* for partitioning methods (NEXT SLIDES)
- An incorrect merge early in the tree cannot be changed later on
- The choice of the distance measure depends on the data and the intention of the clustering
- Even data generated at random will result in a clustering: be careful with interpretation!

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Partitioning

Partitioning algorithms (= non-hierarchical methods)

- split the data into a pre-specified number k of groups
- iteratively re-allocate objects until some optimality criterion is met

k thus needs to be fixed in advance

Examples:

- k-means clustering
- Partitioning around medoids (PAM)
  generalization of k-means (allows additional optimisation criteria)
- Self-organising maps (SOM)
  similar to k-means but with additional constraints (grid-like structure)

Partitioning - *k*-means

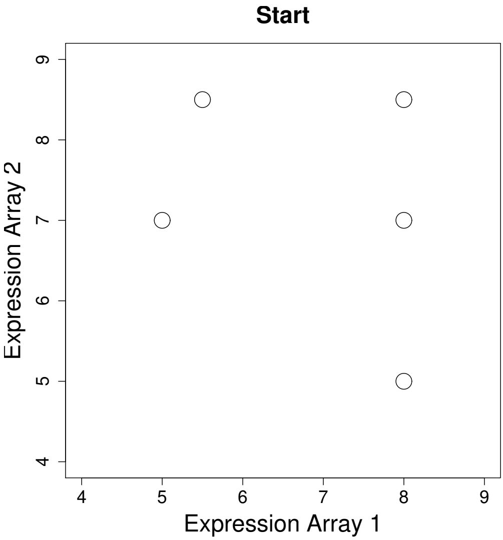
k-means

The *k*-means algorithm minimises the sum of within-cluster variances

It chooses a random sample of k different objects as initial cluster centroids, then alternating until convergence:

1. Assign each object to the cluster whose centroid is closest (among the k centroids) with respect to Euclidean distance
2. Calculate k new centroids as the averages of all points assigned to the same cluster

Partitioning - *k*-means example

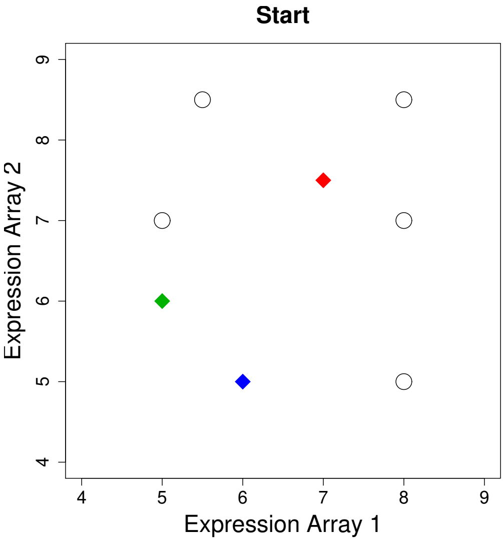


$k = 3$

Expression matrix

$$\begin{pmatrix} 5.0 & 7.0 \\ 5.5 & 8.5 \\ 8.0 & 8.5 \\ 8.0 & 7.0 \\ 8.0 & 5.0 \end{pmatrix}$$

Partitioning - *k*-means example



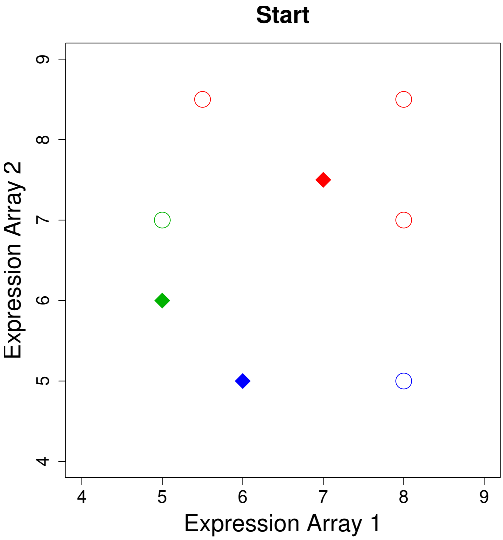
Centroid matrix

$$\begin{pmatrix} 5.0 & 6.0 \\ 7.0 & 7.5 \\ 6.0 & 5.0 \end{pmatrix}$$

Expression matrix

$$\begin{pmatrix} 5.0 & 7.0 \\ 5.5 & 8.5 \\ 8.0 & 8.5 \\ 8.0 & 7.0 \\ 8.0 & 5.0 \end{pmatrix}$$

Partitioning - *k*-means example



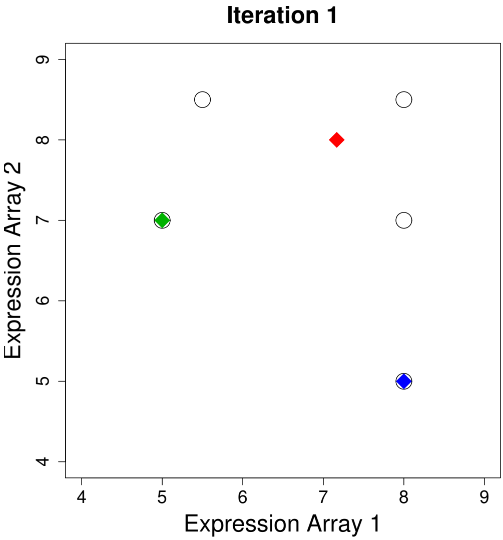
Centroid matrix

$$\begin{pmatrix} 5.0 & 6.0 \\ 7.0 & 7.5 \\ 6.0 & 5.0 \end{pmatrix}$$

Expression matrix

$$\begin{pmatrix} 5.0 & 7.0 \\ 5.5 & 8.5 \\ 8.0 & 8.5 \\ 8.0 & 7.0 \\ 8.0 & 5.0 \end{pmatrix}$$

Partitioning - *k*-means example



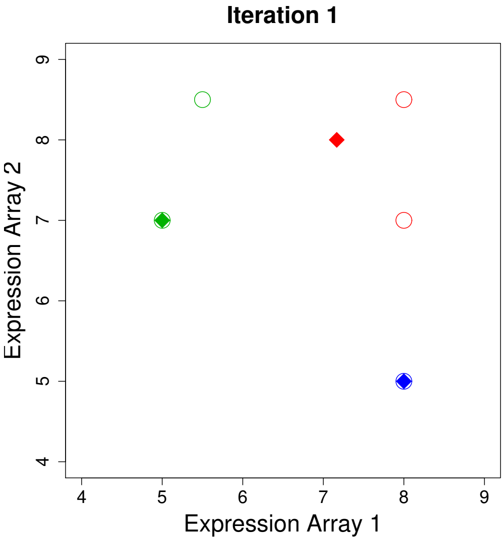
Centroid matrix

$$\begin{pmatrix} \color{green}{5.0} & \color{green}{7.0} \\ \color{red}{7.17} & \color{red}{8.0} \\ \color{blue}{8.0} & \color{blue}{5.0} \end{pmatrix}$$

Expression matrix

$$\begin{pmatrix} 5.0 & 7.0 \\ 5.5 & 8.5 \\ 8.0 & 8.5 \\ 8.0 & 7.0 \\ 8.0 & 5.0 \end{pmatrix}$$

Partitioning - *k*-means example



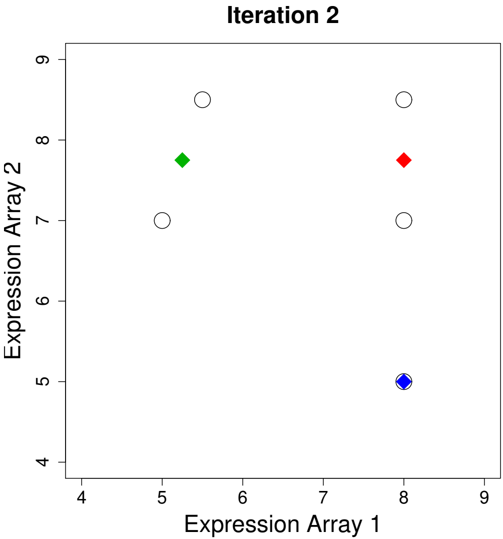
Centroid matrix

$$\begin{pmatrix} 5.0 & 7.0 \\ 7.17 & 8.0 \\ 8.0 & 5.0 \end{pmatrix}$$

Expression matrix

$$\begin{pmatrix} 5.0 & 7.0 \\ 5.5 & 8.5 \\ 8.0 & 8.5 \\ 8.0 & 7.0 \\ 8.0 & 5.0 \end{pmatrix}$$

Partitioning - *k*-means example



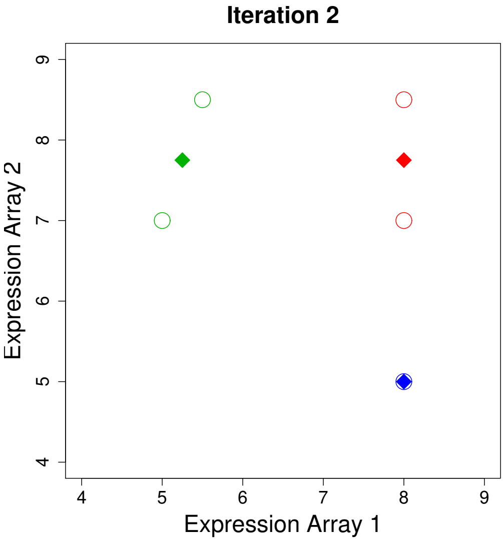
Centroid matrix

$$\begin{pmatrix} 5.25 & 7.75 \\ 8.00 & 7.75 \\ 8.0 & 5.0 \end{pmatrix}$$

Expression matrix

$$\begin{pmatrix} 5.0 & 7.0 \\ 5.5 & 8.5 \\ 8.0 & 8.5 \\ 8.0 & 7.0 \\ 8.0 & 5.0 \end{pmatrix}$$

Partitioning - *k*-means example



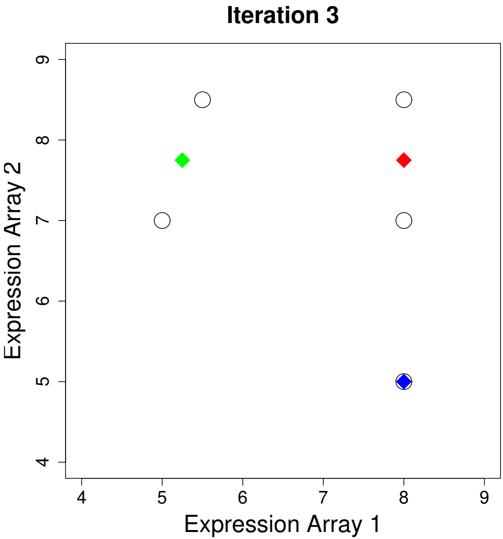
Centroid matrix

$$\begin{pmatrix} 5.25 & 7.75 \\ 8.00 & 7.75 \\ 8.0 & 5.0 \end{pmatrix}$$

Expression matrix

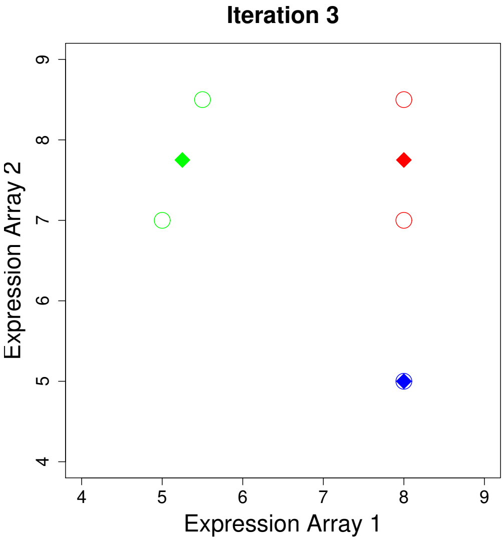
$$\begin{pmatrix} 5.0 & 7.0 \\ 5.5 & 8.5 \\ 8.0 & 8.5 \\ 8.0 & 7.0 \\ 8.0 & 5.0 \end{pmatrix}$$

Partitioning - *k*-means example



Iteration 3: No changes in centroid matrix

Partitioning - *k*-means example



Iteration 3: No changes
→ We are done.

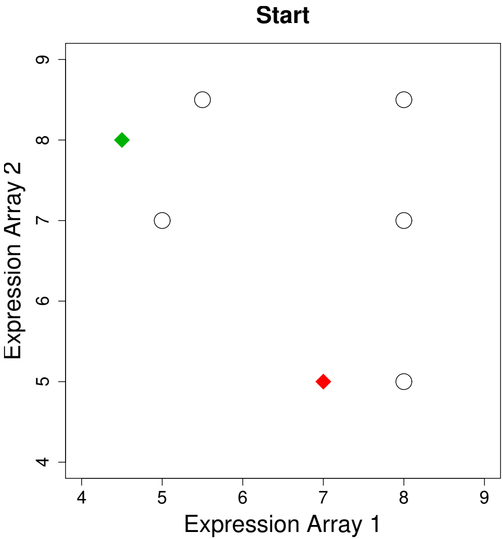
Partitioning - *k*-means

Choice of cluster number and initial starting values for cluster centroids:

- Changing the number of clusters can completely change the cluster structure. This is contrary to hierarchical clustering.
- *k*-means is a randomised algorithm: two runs usually produce different results. Thus, it has to be applied several times and the result with minimal sum of within-cluster-variances should be chosen.
  Even when doing so, we are not guaranteed to find the best solution.

Example: same data set (5 patients, 2 expression values)
Method: **Partitioning clustering** with *k*-**means** with $k = 2$

Partitioning - *k*-means example 2



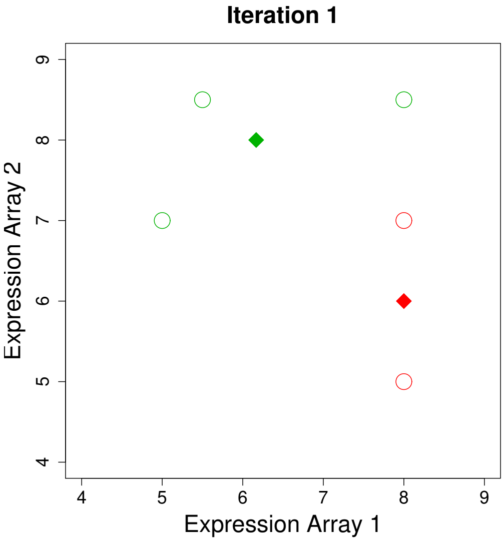
Centroid matrix

$$\begin{pmatrix} 4.5 & 8.0 \\ 7.0 & 5.0 \end{pmatrix}$$

Expression matrix

$$\begin{pmatrix} 5.0 & 7.0 \\ 5.5 & 8.5 \\ 8.0 & 8.5 \\ 8.0 & 7.0 \\ 8.0 & 5.0 \end{pmatrix}$$

Partitioning - *k*-means example 2



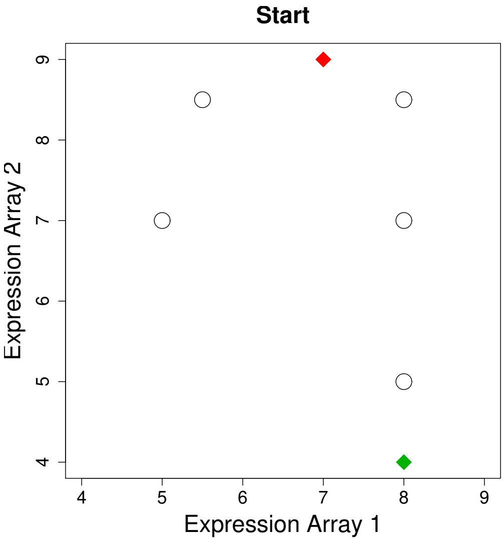
Centroid matrix

$$\begin{pmatrix} 6.17 & 8.0 \\ 8.0 & 6.0 \end{pmatrix}$$

Expression matrix

$$\begin{pmatrix} 5.0 & 7.0 \\ 5.5 & 8.5 \\ 8.0 & 8.5 \\ 8.0 & 7.0 \\ 8.0 & 5.0 \end{pmatrix}$$

Partitioning - *k*-means example 3



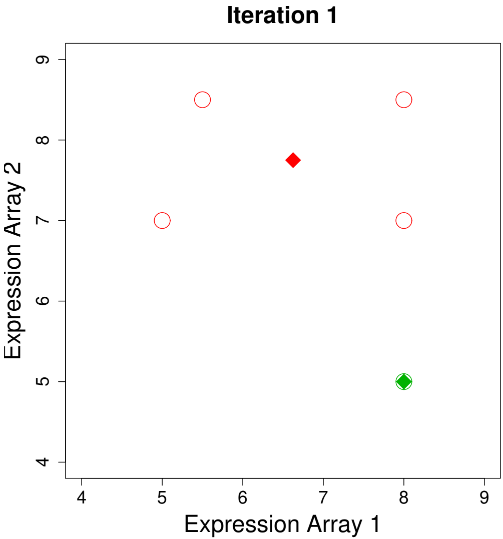
Centroid matrix

$$\begin{pmatrix} 8.0 & 4.0 \\ 7.0 & 9.0 \end{pmatrix}$$

Expression matrix

$$\begin{pmatrix} 5.0 & 7.0 \\ 5.5 & 8.5 \\ 8.0 & 8.5 \\ 8.0 & 7.0 \\ 8.0 & 5.0 \end{pmatrix}$$

Partitioning - *k*-means example 3



Centroid matrix

$$\begin{pmatrix} 8.0 & 5.0 \\ 6.63 & 7.75 \end{pmatrix}$$

Expression matrix

$$\begin{pmatrix} 5.0 & 7.0 \\ 5.5 & 8.5 \\ 8.0 & 8.5 \\ 8.0 & 7.0 \\ 8.0 & 5.0 \end{pmatrix}$$

1. Introduction
   - Motivation
   - Notions of similarity
2. Hierarchical Clustering Algorithms
   - Main ideas
   - Illustrative example
   - Visualization
   - Summary
3. Partitioning clustering: *k*-means
   - Partitioning Clustering Algorithms
   - Main idea of the *k*-means
   - Illustrative example 1
   - Illustrative example 2
4. **Summary**

Clustering - Summary

Hierarchical clustering:

- Procedure provides a hierarchy of the clustering, with the number of clusters ranging from 1 to the number of objects
- Incorrect merges early in the tree cannot be changed later on
- Careful with interpretation of dendrograms and resulting heatmaps! The order of objects within a cluster is arbitrary

Partitioning algorithms:

- Careful with initalization...
- How to choose the correct number of groups?

Clustering - Summary

All clustering methods:

- The choice of the distance measure depends on the data and the intention of the clustering
- Use objective measures to support the decision for number of clusters
- Even data generated at random will result in clusters
- Be careful with pre-selection of features before clustering!

Practical Issues in Clustering

- Some decisions to be made:
  - Should the variables be standardized first? Other transformations needed to achieve normally distributed data?
  - Do we need a pre-selection of variables? This needs to be unsupervised, i.e. using variances not t-tests
- In case of hierarchical clustering:
  - What dissimilarity measure should be used?
  - What type of linkage should be used?
  - Where should we cut the dendrogram in order to obtain clusters?
- In case of partitioning clustering:
  - How many clusters should we look for?
- Try several choices, and look for clustering results that are most useful for interpretation. There is no single right answer!

R/ Bioconductor

Heatmaps

- heatmap() (stats) and many enhancements, e.g. pheatmap() (pheatmap) and Heatmap() (ComplexHeatmap)

Hierarchical clustering

- hclust() (stats), hcluster (amap)

Partitioning clustering

- kmeans() (stats), pam() (cluster)

CRAN Task View Cluster

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