Machine Learning for Bioinformatics & Systems Biology

2. Classification and clustering

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Some material courtesy of Robert Duin and David Tax

Classification

- Logistic classifier
- Plug-in Bayes classifiers
  - Density-based classification: Parzen, nearest neighbour, Gaussian
- Decision trees and random forests

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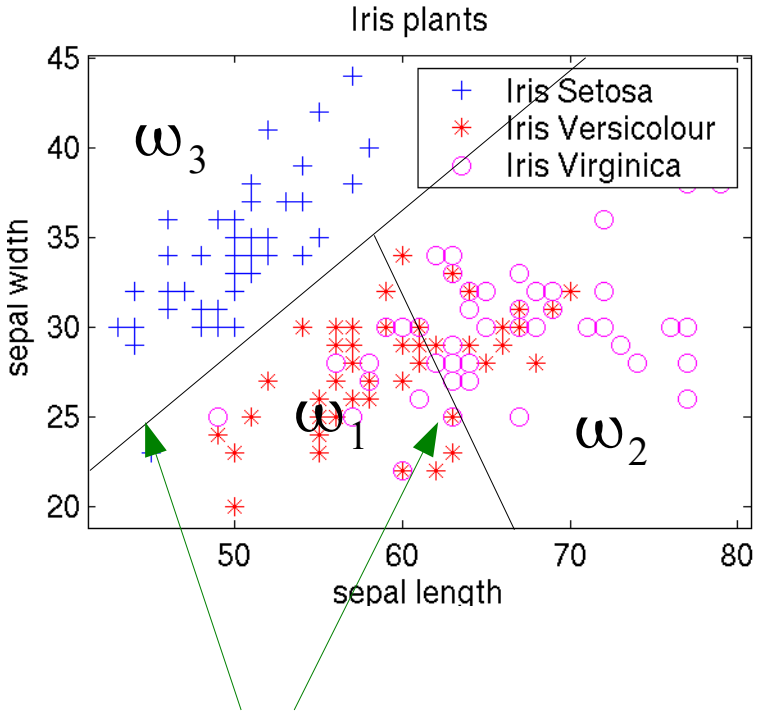
Classification (2)

- Given labeled data: $\boldsymbol{x}$
- Assign to each object a class label ω
- In effect splits the feature space in separate regions



Description of a classifier

There are several ways to describe the classifier:

- If $p(\omega=h|\mathbf{x})>p(\omega=d|\mathbf{x})$ then assign to h otherwise to d
- If $p(\omega=h|\mathbf{x})-p(\omega=d|\mathbf{x})>0$ then assign to h
- If $\frac{p(\omega=h|\mathbf{x})}{p(\omega=d|\mathbf{x})}>1$ then assign to h
- If $\ln(p(\omega=h|\mathbf{x}))-\ln(p(\omega=d|\mathbf{x}))>0$ then assign to h

A Bayesian classifier is a *threshold* on the difference between *posterior probabilities*

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Logistic classifier

- We can rewrite:

$$\ln\left(p(\omega=h|\boldsymbol{x})\right)-\ln\left(p(\omega=d|\boldsymbol{x})\right)=\ln\left(\frac{p(\omega=h|\boldsymbol{x})}{p(\omega=d|\boldsymbol{x})}\right)$$

logit, log-odds

- Assume we can approximate:

$$\ln\left(\frac{p(\omega=h|\boldsymbol{x})}{p(\omega=d|\boldsymbol{x})}\right)=w_0+\boldsymbol{w}^T\boldsymbol{x}$$

- The classifier becomes (computer lab exercise):

$$p(\omega=d|\boldsymbol{x})=\frac{1}{1+\exp(\boldsymbol{w}^T\boldsymbol{x}+w_0)}$$

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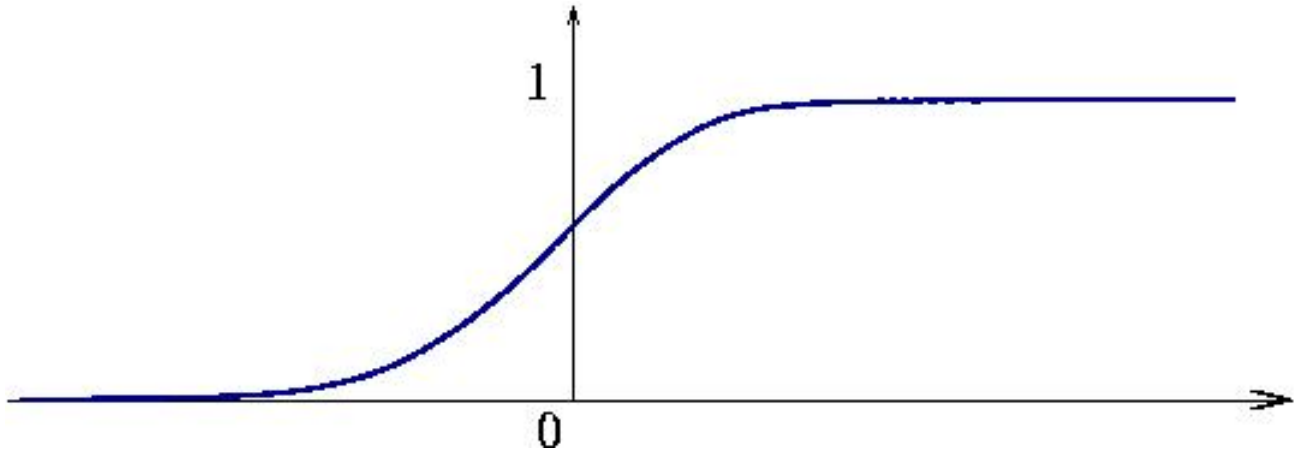
Logistic function

- The function looks like:



$$f(x)=\frac{1}{1+\exp(-x)}$$

logistic (sigmoid) function

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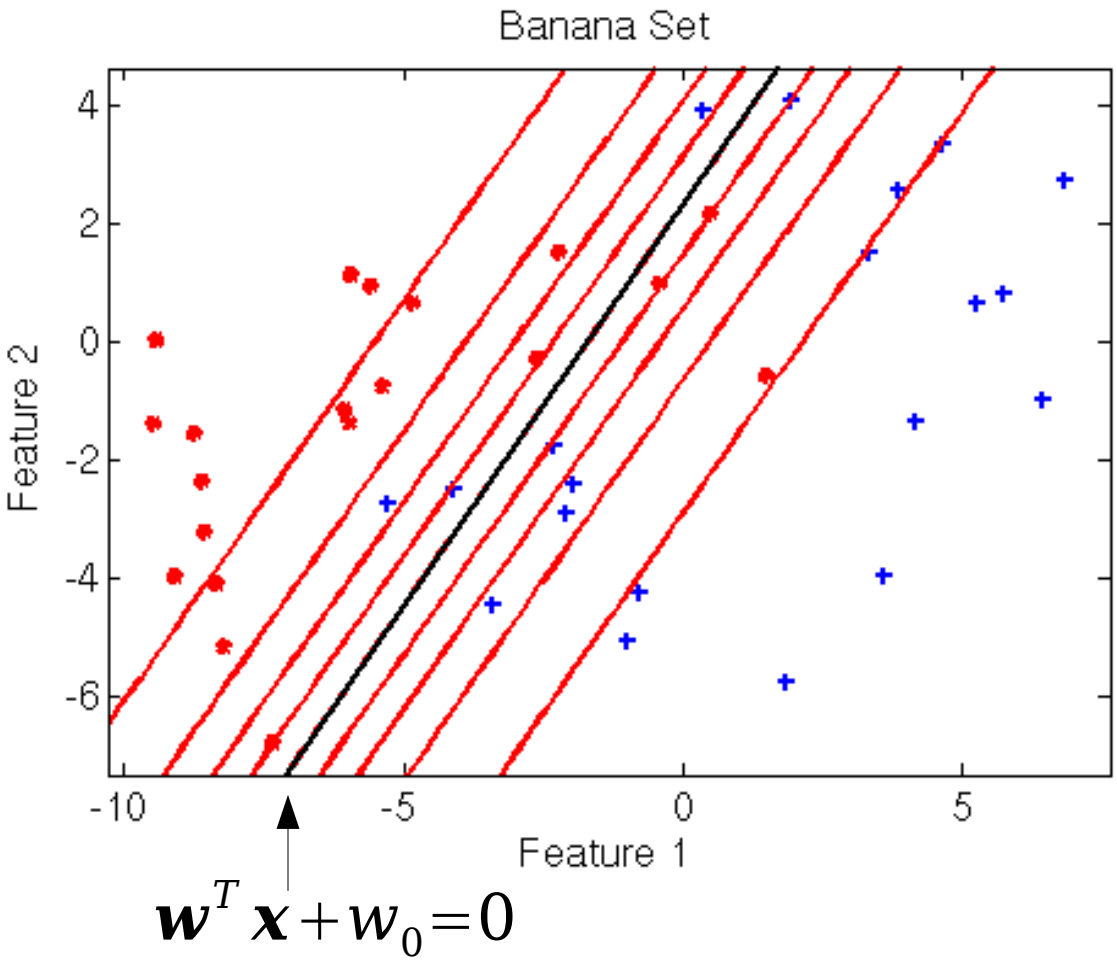
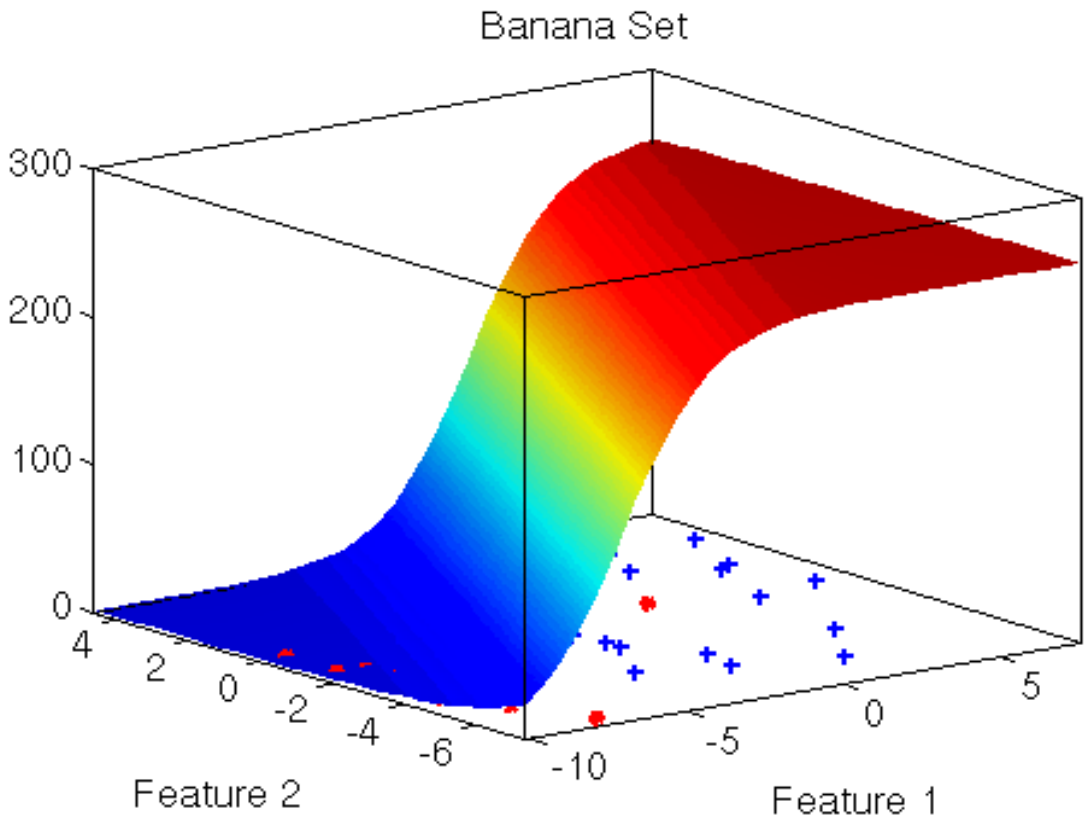
Logistic classifier (2)

- On a two-dimensional dataset it looks like:



Logistic classifier (3)

- On a two-dimensional dataset it looks like:



Optimizing the logistic classifier

- To optimize the parameters on a training set, maximize the likelihood

$$L = \prod_{i=1}^{n_1} p(\mathbf{x}_i^{(1)} | \omega_1) \prod_{j=1}^{n_2} p(\mathbf{x}_j^{(2)} | \omega_2)$$

where $\mathbf{x}_i^{(j)}$ is the i-th object from class j

- Maximization using gradient ascent
- Appears to be easier to maximize log(L)
- Weights are iteratively updated as:

$$\mathbf{w}_{new} = \mathbf{w}_{old} + \eta \frac{\partial \log(L)}{\partial \mathbf{w}}$$

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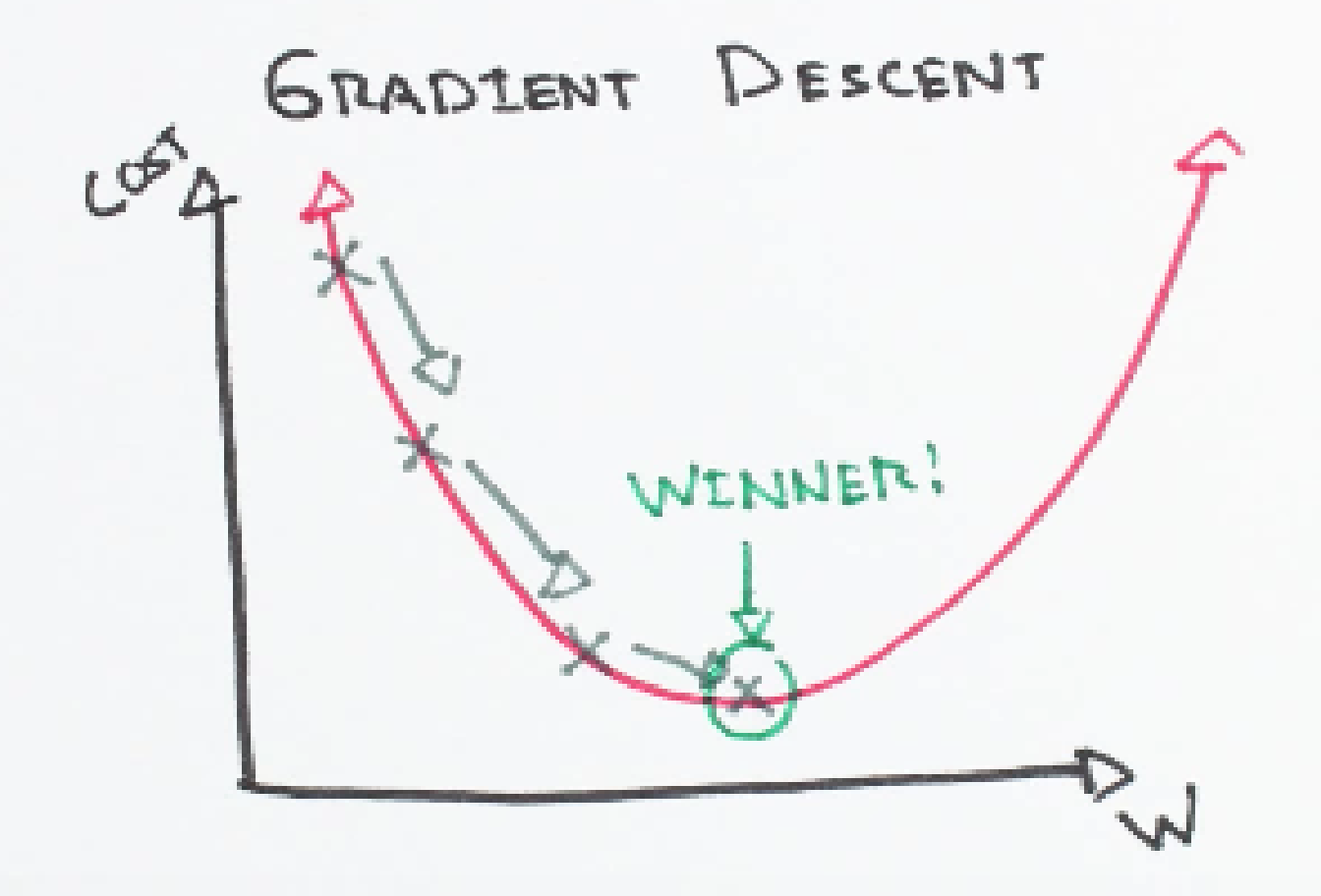
GRADIENT DESCENT
LOSS
WINNER!
W

Optimizing the logistic classifier (2)

- Function to maximize

$$L = \prod_{i=1}^{n_1} p(\boldsymbol{x}_i^{(1)}|\omega_1) \prod_{j=1}^{n_2} p(\boldsymbol{x}_j^{(2)}|\omega_2)$$

- Use log(L)

$$\log(L) = \sum_{i=1}^{n_1} \log(p(\boldsymbol{x}_i^{(1)}|\omega_1)) + \sum_{j=1}^{n_2} \log(p(\boldsymbol{x}_j^{(2)}|\omega_2))$$

- Use Bayes' theorem

$$\log p(\boldsymbol{x}_i^{(1)}|\omega_1) = \log p(\omega_1|\boldsymbol{x}_i^{(1)}) - \log p(\omega_1) + \log p(\boldsymbol{x}_i^{(1)})$$

constant

- Therefore

$$\log(L) = \sum_{i=1}^{n_1} \log(p(\omega_1|\boldsymbol{x}_i^{(1)})) + \sum_{j=1}^{n_2} \log(p(\omega_2|\boldsymbol{x}_j^{(2)})) + C$$

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Optimizing the logistic classifier (3)

- Filling in that

$$p(\omega_2|\boldsymbol{x}) = \frac{1}{1+\exp(\boldsymbol{w}^T\boldsymbol{x}+w_0)}$$

gives

$$\log(L) = \sum_{i=1}^{n_1}(w_0+\boldsymbol{w}^T\boldsymbol{x}_i^{(1)}) - \sum_{j=1}^{n_1+n_2}\log(1+\exp(w_0+\boldsymbol{w}^T\boldsymbol{x}_j))$$

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Derivative of the log-likelihood

- The gradient of log(L) is

$$\frac{\partial \log(L)}{\partial w_0} = n_1 - \sum_{i=1}^{n_1+n_2} p(\omega_1|\boldsymbol{x}_i)$$

$$\frac{\partial \log(L)}{\partial w_j} = \sum_{i=1}^{n_1} (\boldsymbol{x}_i^{(1)})_j - \sum_{i=1}^{n_1+n_2} p(\omega_1|\boldsymbol{x}_i)(\boldsymbol{x}_i)_j, \; j=1,\ldots,p$$

- Take initial values: $w_0 = 0, \boldsymbol{w} = \boldsymbol{0}$
- Keep iterating $\boldsymbol{w}_{new} = \boldsymbol{w}_{old} + \eta \frac{\partial \log(L)}{\partial \boldsymbol{w}}$

till convergence

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Plug-in Bayes classification

- In many cases the posterior is hard to estimate
- Often a functional form of the class distributions can be assumed
- Use Bayes' theorem to rewrite one into the other:

$$p(\omega|\mathbf{x}) = \frac{p(\mathbf{x}|\omega)\,p(\omega)}{p(\mathbf{x})}$$

class-conditional distribution: $p(\mathbf{x}|\omega)$

prior distribution: $p(\omega)$

data distribution: $p(\mathbf{x})$

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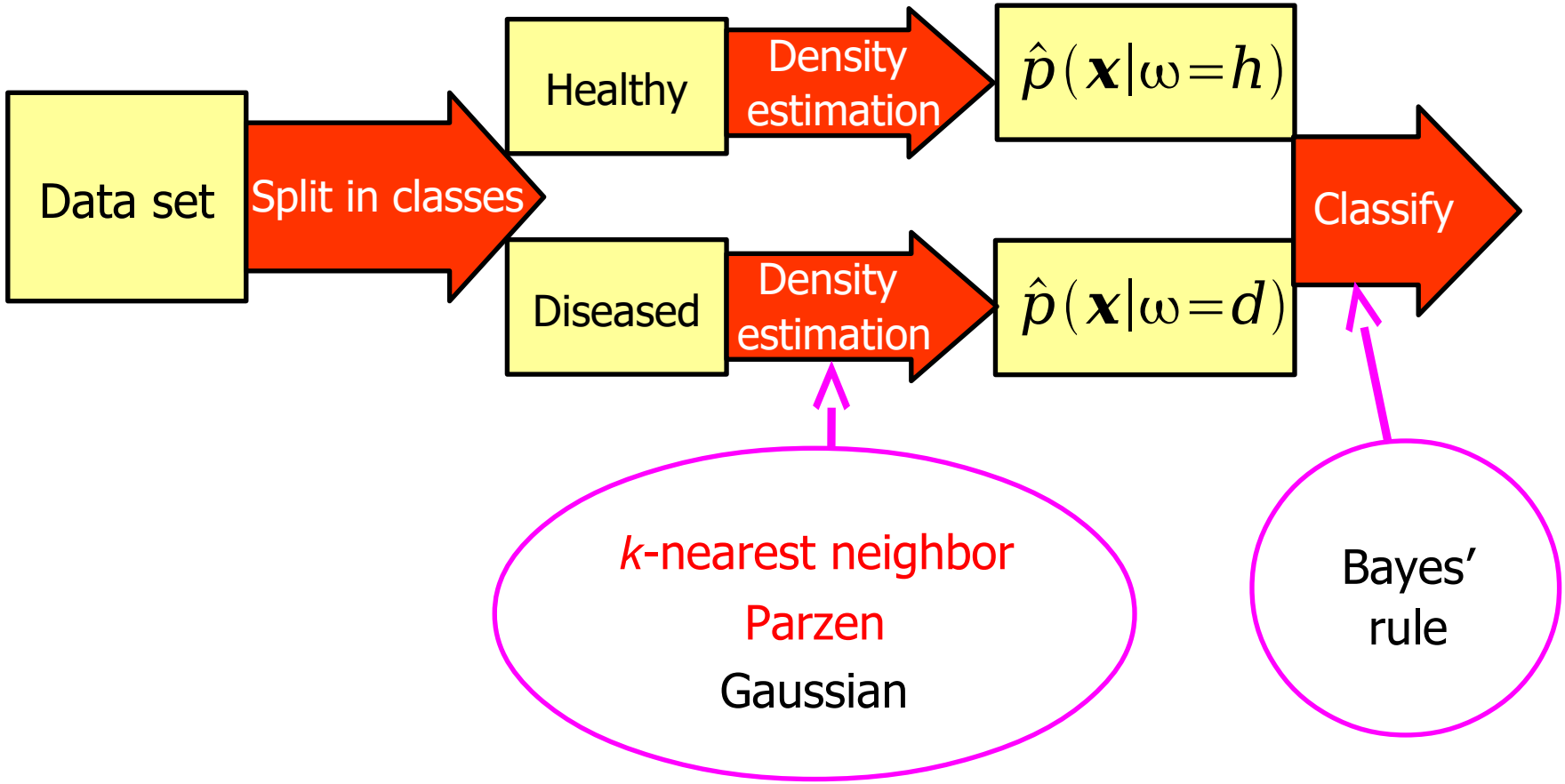
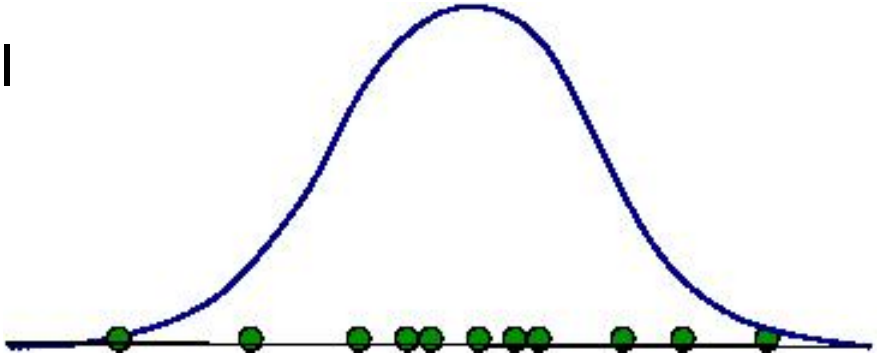
Plug-in Bayes classification (2)



Bayes decision making

$$\hat{p}(\boldsymbol{x}|\omega_i) = N(\boldsymbol{x}; \mu, \sigma)$$

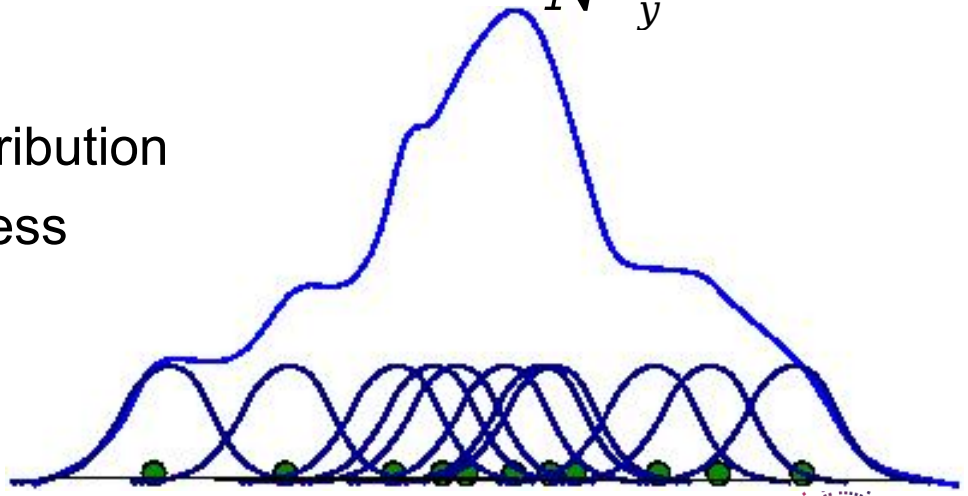
- Estimate the class-conditional density (Day 1) $\hat{p}(\boldsymbol{x}|\omega_i)$



- Parametric
  - Known distribution
  - Estimate parameters on training set

$$\hat{p}(\boldsymbol{x}|\omega_i) = \frac{1}{N}\sum_{y} K(\boldsymbol{x}, \boldsymbol{y})$$

- Non-parametric
  - No knowledge on distribution
  - Manage the smoothness of the distribution



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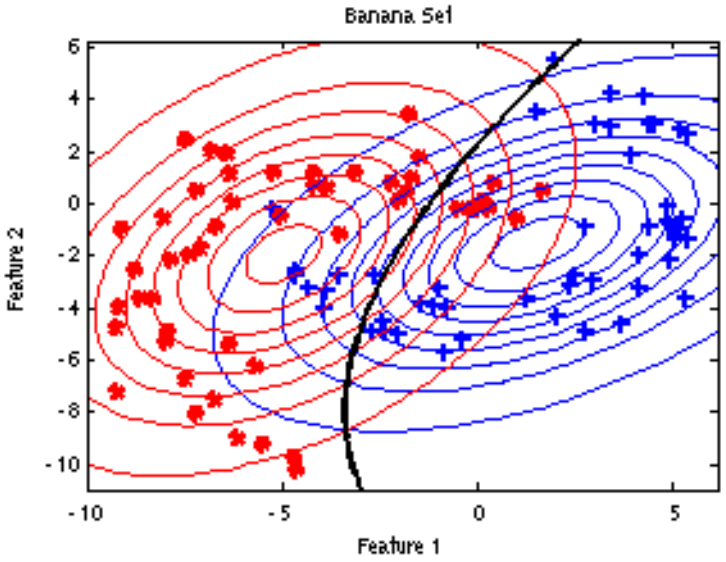
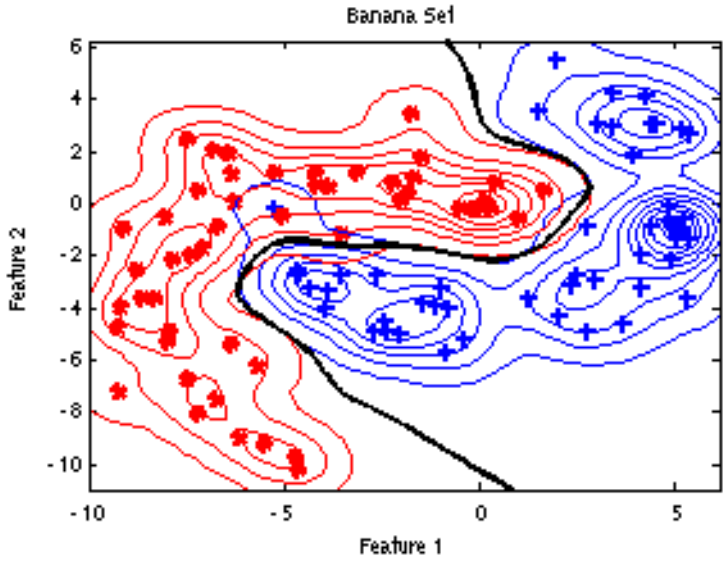
Example plugin

- Two examples

Normal density estimation



Parzen density estimation



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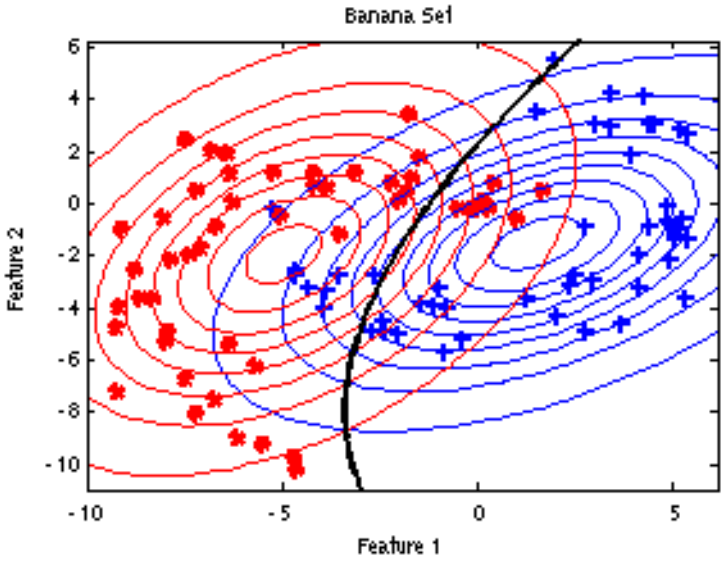
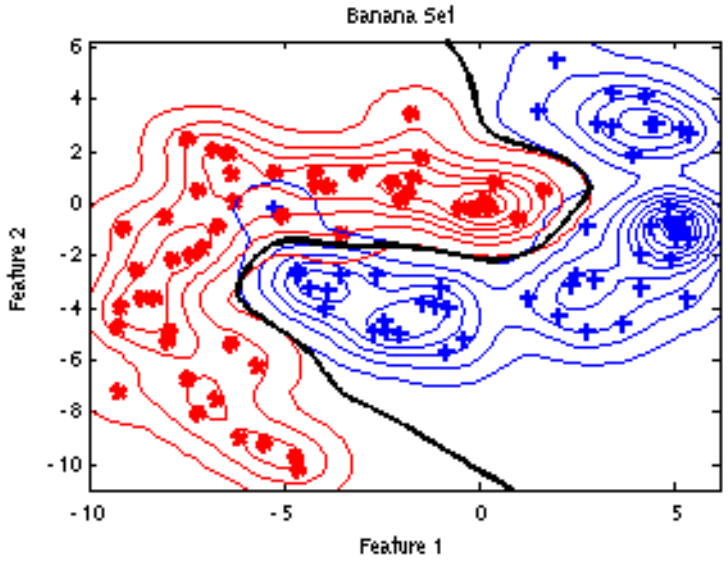
Example plugin

- Two examples

Normal density estimation



Parzen density estimation



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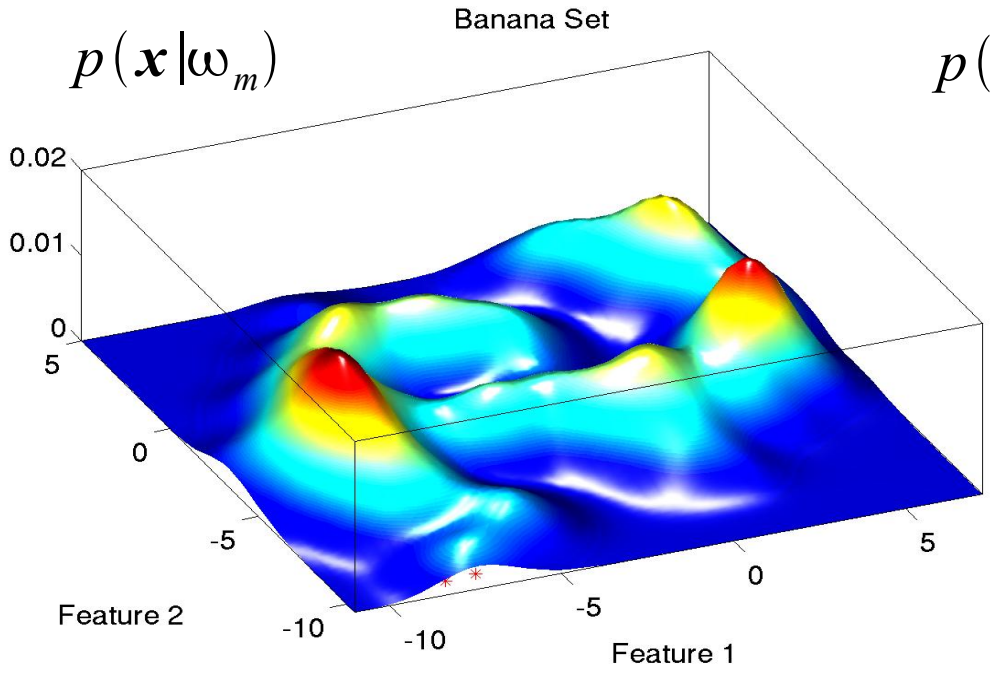
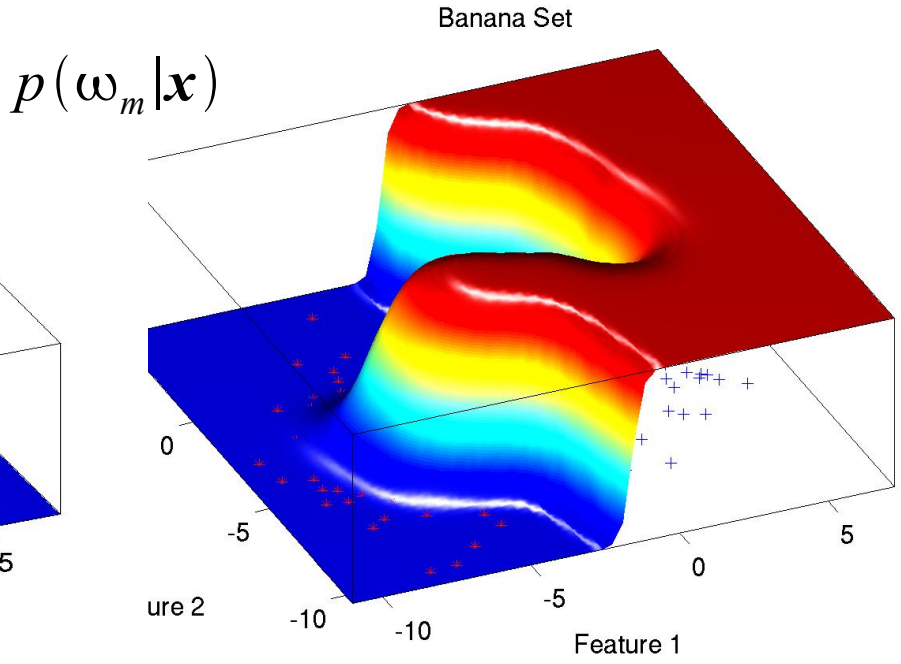
Parzen classifier

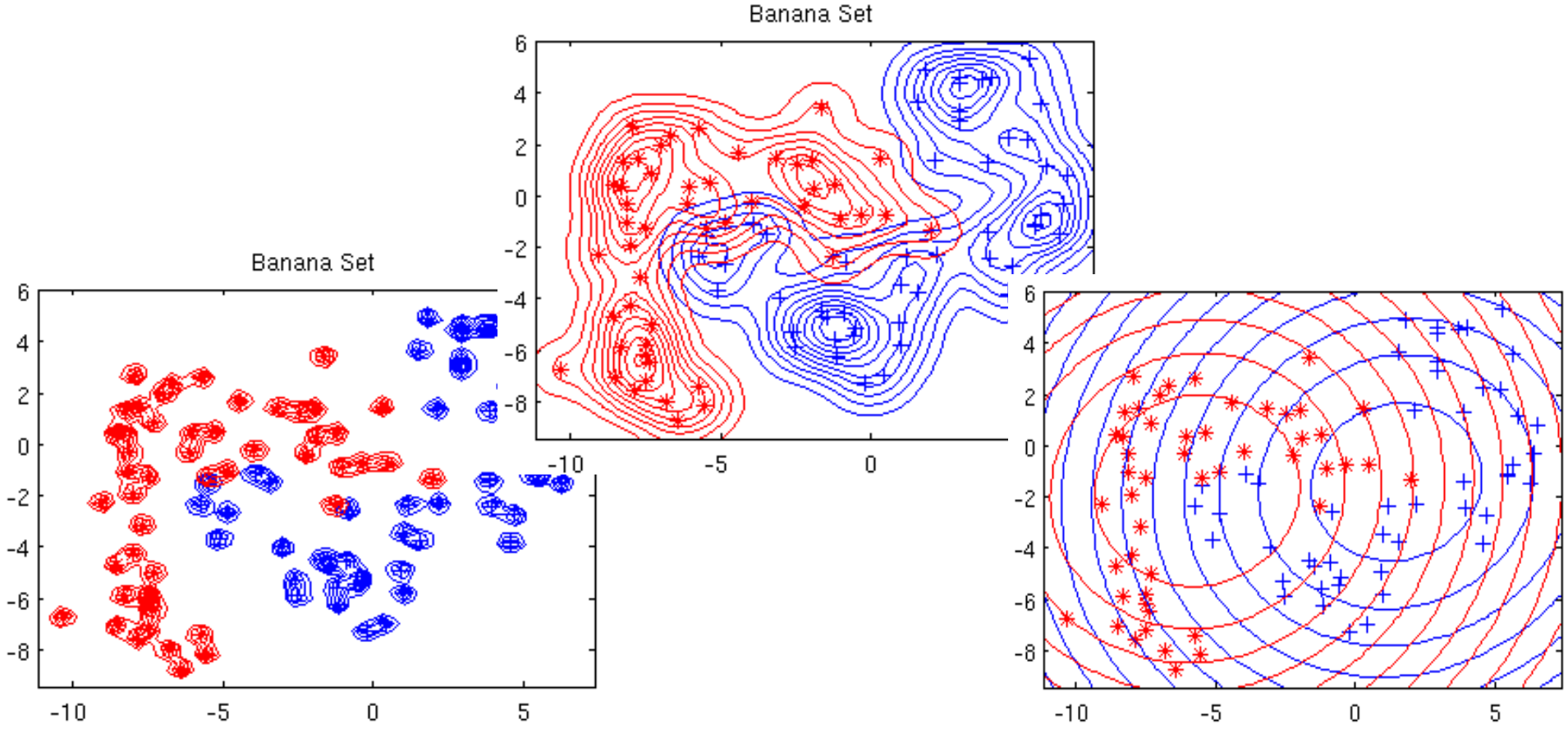
$$p(\boldsymbol{x}|\omega_m) = \frac{1}{N}\sum_{i=1}^{N_m} N(\boldsymbol{x}; \boldsymbol{x}_i, h\boldsymbol{I})$$





Parzen width parameter

- The width parameter *h* has a large influence



Optimization of *h*

- Use the average *k*-nearest neighbor distance
  (*k*=10 is suggested...)
- Use a heuristic $$h = \sigma \left(\frac{4}{p+2} \right)^{\frac{1}{p+4}} n^{\frac{-1}{p+4}}$$

$$\sigma^2 = \frac{1}{p} \sum_{i=1}^{p} s_{ii}$$

- Optimize the likelihood using cross-validation

$$\prod_{i=1}^{n} \hat{p}(\boldsymbol{x}_i)$$

- and more...

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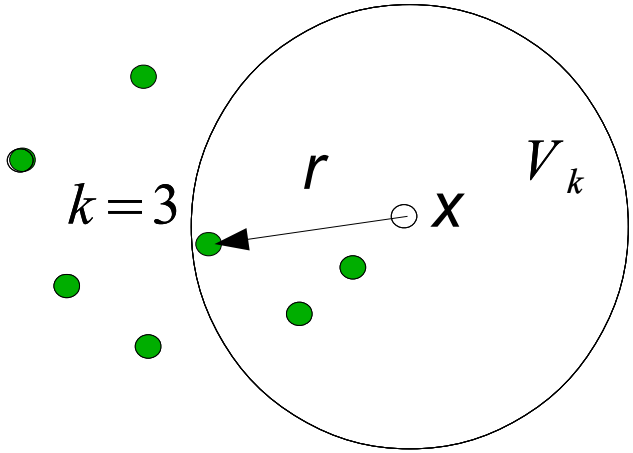
Nearest neighbor classification

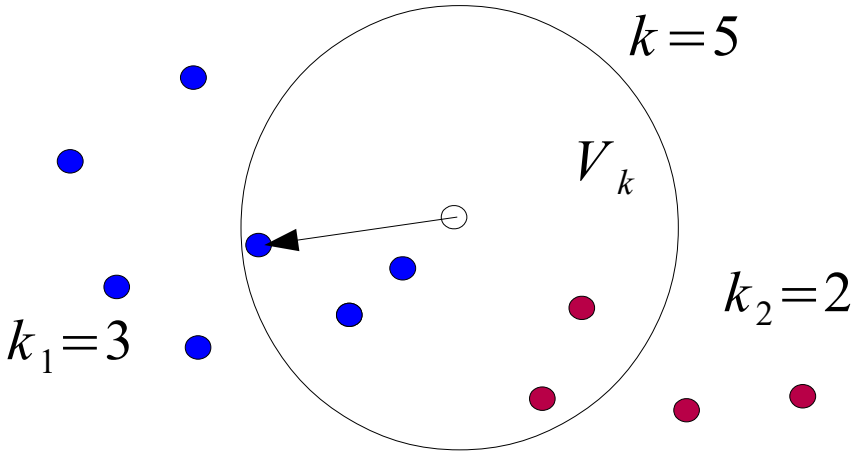


- For the k-nearest neighbor density we defined:

$$\hat{p}(\boldsymbol{x}) = \frac{k}{n V_k}$$

where V_k is the volume of the sphere centered at x, with radius r the distance to the k-th nearest neighbor

Nearest neighbor classification (2)



- When more classes are present, count how many objects of each of the classes are members of the *k* neighbors
- Class-conditional density:

$$\hat{p}(\boldsymbol{x}|\omega_m)=\frac{k_m}{n_m V_k}$$

Nearest neighbor classification (3)

- Using Bayes: $\hat{p}(\boldsymbol{x}|\omega_m)\,\hat{p}(\omega_m) \geq \hat{p}(\boldsymbol{x}|\omega_i)\,\hat{p}(\omega_i)$
- Estimate the prior probability by counting:

$$\hat{p}(\omega_m) = \frac{n_m}{n}$$

- Fill in:

$$\frac{k_m}{n_m V_k}\frac{n_m}{n} \geq \frac{k_i}{n_i V_k}\frac{n_i}{n} \quad \Rightarrow \quad k_m \geq k_i$$

- No density estimation is needed!

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The choice of *k*

- When does the classifier become more smooth? When more ragged?

- What happens for $k = 1$, and $k = n$?

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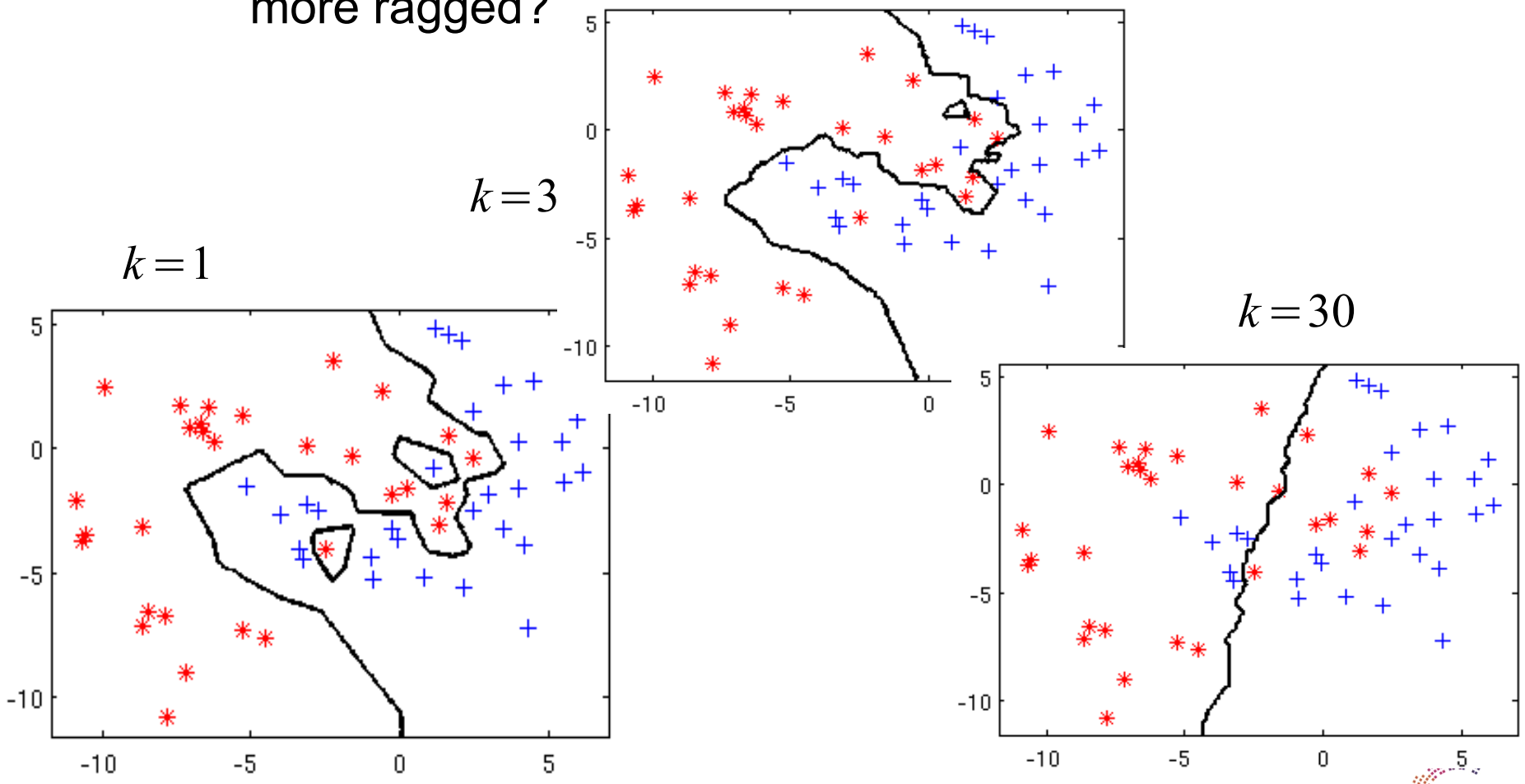
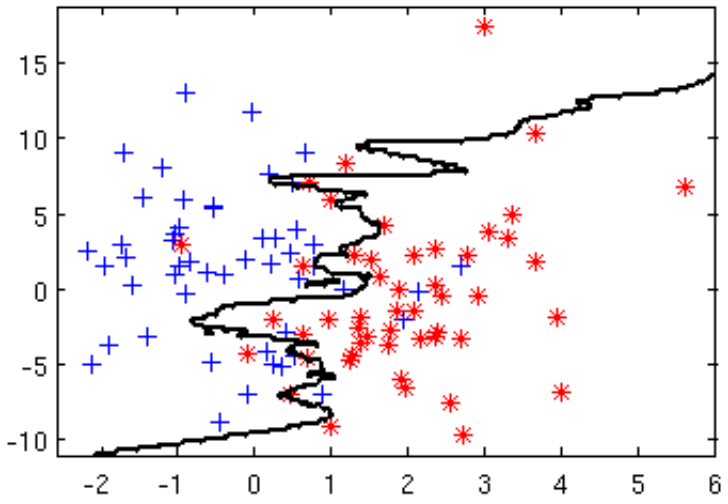
The choice of *k* (2)

- When does the classifier become more smooth? When more ragged?



Sometimes strange results:

$k = 5$



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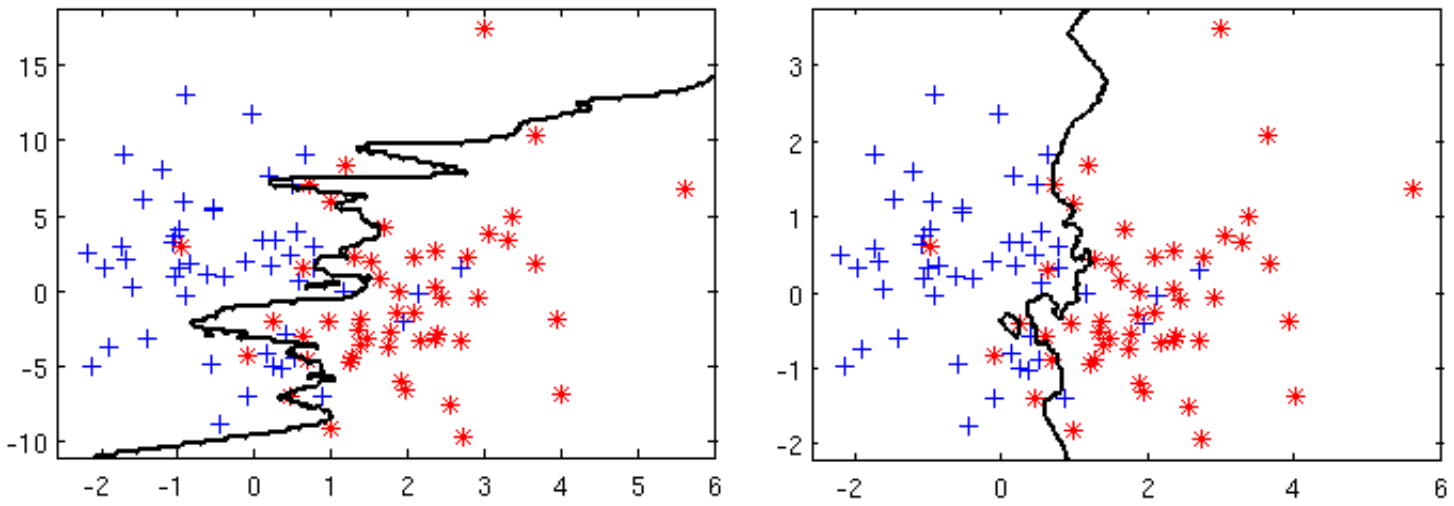
Sometimes strange results (2):

$k = 5$



Rescaling the features has large influence!

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Advantages/disadvantages

- simple and flexible classifier
- often a very good classification performance
- it is simple to adapt the complexity of the classifier

- you have to store the complete training set
- distances to all training objects have to be computed
- scaling of the features should be sensible
- you have to optimize *k* or *h*

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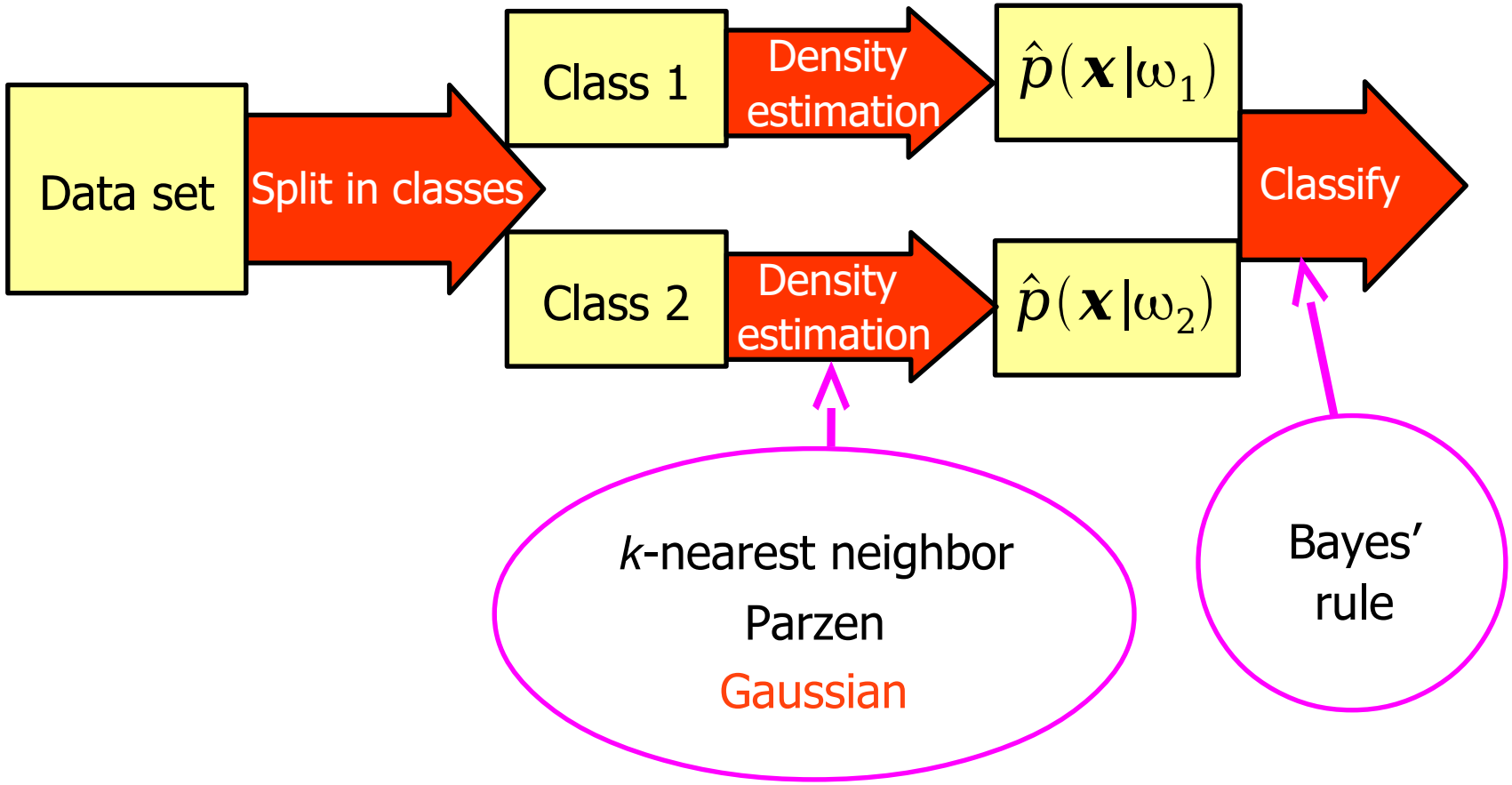
Classifying with densities



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Plug-in Gaussian distribution

- Now take the most obvious choice: the Gaussian distribution

$$\hat{p}(\mathbf{x}|\omega) = \frac{1}{\sqrt{2\pi^p det(\hat{\Sigma}_\omega)}} \exp\left(-\frac{1}{2}(\mathbf{x}-\hat{\mu}_\omega)^T \hat{\Sigma}_\omega^{-1}(\mathbf{x}-\hat{\mu}_\omega)\right)$$

- So-called parametric density estimation
- We have to estimate the parameters via maximum likelihood:

$$\hat{\mu} = \frac{1}{n}\sum_{i=1}^{n} \mathbf{x}_i$$

$$\hat{\Sigma} = \frac{1}{n}\sum_{i=1}^{n} (\mathbf{x}_i - \hat{\mu})(\mathbf{x}_i - \hat{\mu})^T$$

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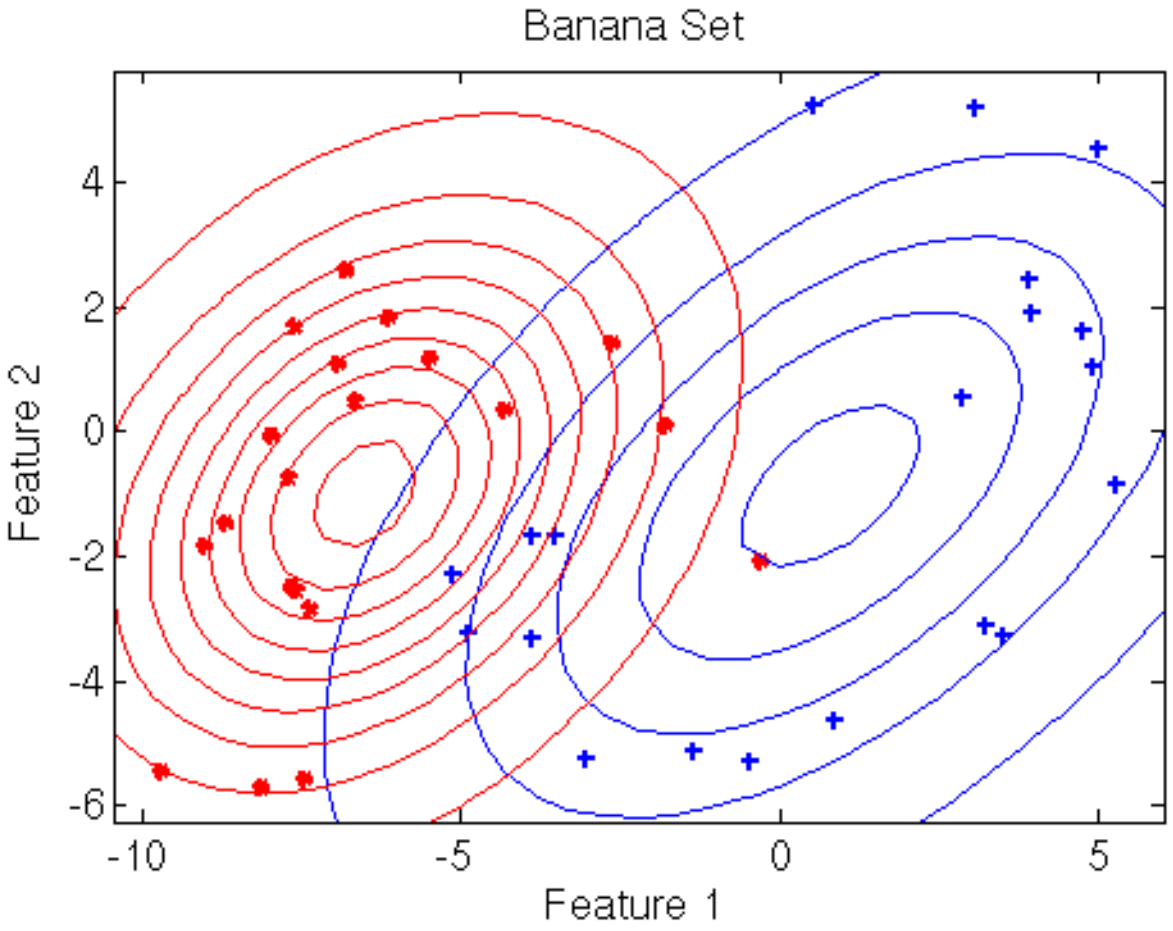
Example on banana data

- A single Gaussian distribution on each class:



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Class-conditional densities

- Combining

$$\hat{p}(\mathbf{x}|\omega_i) = \frac{1}{\sqrt{2\pi^p det(\Sigma_i)}} \exp\left(-\frac{1}{2}(\mathbf{x}-\mu_i)^T \Sigma_i^{-1}(\mathbf{x}-\mu_i)\right)$$

$$p(\omega|\mathbf{x}) = \frac{p(\mathbf{x}|\omega)\,p(\omega)}{p(\mathbf{x})}$$

we can derive for log(p):

$$\log(\hat{p}(\omega_i|\mathbf{x})) = -\frac{p}{2}\log(2\pi) - \frac{1}{2}\log(det\,\Sigma_i)$$

$$-\frac{1}{2}(\mathbf{x}-\mu_i)^T \Sigma_i^{-1}(\mathbf{x}-\mu_i) + \log(p(\omega_i)) - \log(p(\mathbf{x}))$$

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Normal density-based classifier

- $p(\mathbf{x})$ is independent of the classes and can be dropped

$$g_i(\mathbf{x}) = -\frac{1}{2}\log(det\,\Sigma_i) - \frac{1}{2}(\mathbf{x}-\mu_i)^T\Sigma_i^{-1}(\mathbf{x}-\mu_i) + \log(p(\omega_i))$$

- Classifier becomes:

assign $\mathbf{x}$ to class ω_i when for all $i \neq j$: $g_i(\mathbf{x}) > g_j(\mathbf{x})$

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The two-class case

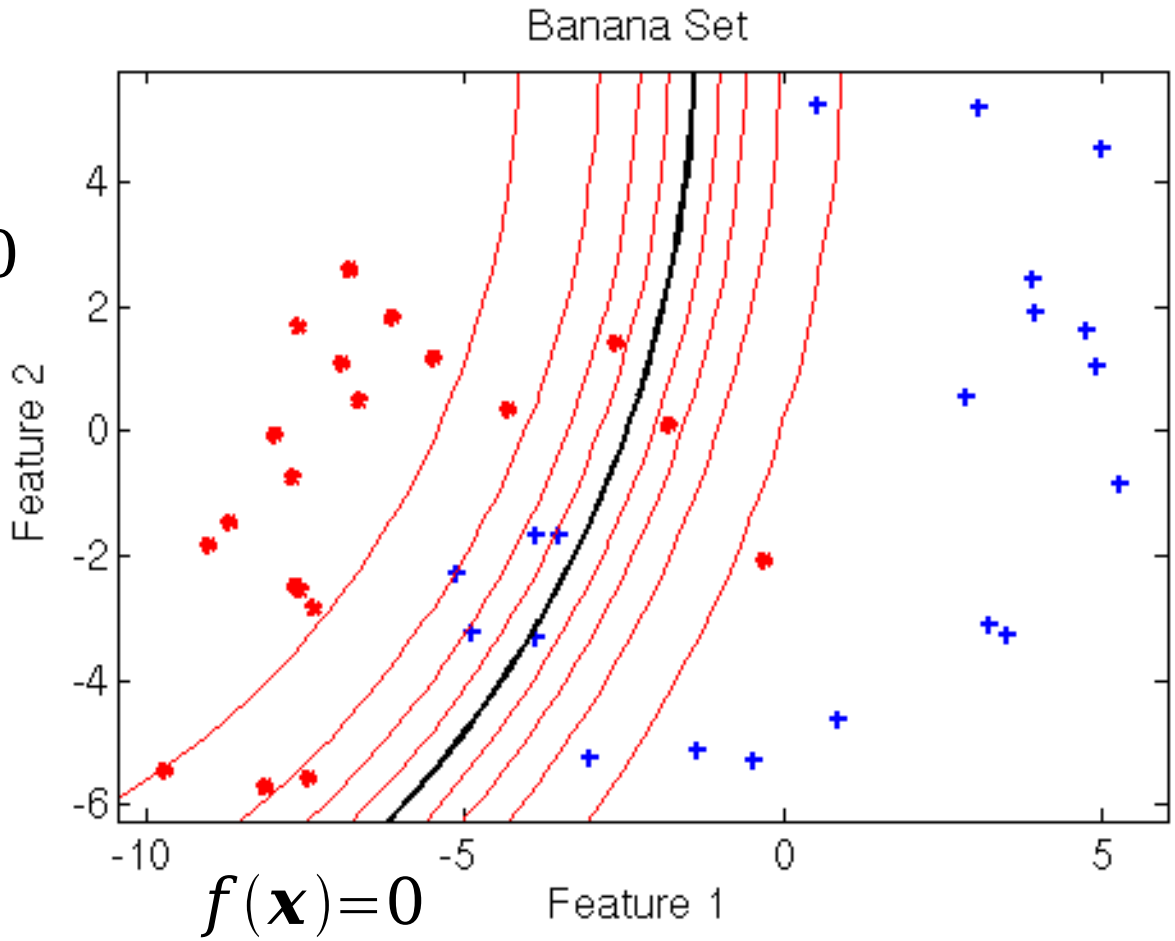
- Define the discriminant $f(\boldsymbol{x}) = p(\omega_1|\boldsymbol{x}) - p(\omega_2|\boldsymbol{x}) > 0$
- We get (computer lab exercise):

$$f(\boldsymbol{x}) = \boldsymbol{x}^T \boldsymbol{W} \boldsymbol{x} + \boldsymbol{w}^T \boldsymbol{x} + w_0$$

- This is a quadratic classifier because
  the decision boundary is a quadratic function of x

Quadratic classifier on banana data

$f(\mathbf{x})>0$



$f(\mathbf{x})<0$

$f(\mathbf{x})=0$

Estimating the covariance matrix

- For the quadratic classifier you need to estimate

$$\hat{\boldsymbol{\Sigma}}_{\boldsymbol{k}} = \frac{1}{n} \sum_{i=1}^{n} (\boldsymbol{x}_i - \hat{\mu}_k)(\boldsymbol{x}_i - \hat{\mu}_k)^T$$

  for each of the classes!

- When you have insufficient data, this covariance matrix cannot be inverted
- Average over the covariance matrices of different classes:

$$\hat{\boldsymbol{\Sigma}} = \frac{1}{c} \sum_{k=1}^{c} \hat{\boldsymbol{\Sigma}}_{\boldsymbol{k}}$$

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Average covariance matrix

- When we use the averaged covariance matrix:

$$g_i(\boldsymbol{x}) = -\frac{1}{2}\log(det\,\hat{\Sigma}) - \frac{1}{2}(\boldsymbol{x}-\hat{\mu}_i)^T\hat{\Sigma}^{-1}(\boldsymbol{x}-\hat{\mu}_i) + \log(p(\omega_i))$$

- First term and quadratic term are always the same for all classes
- We end up with:

$$g_i(\boldsymbol{x}) = -\frac{1}{2}\hat{\mu}_i^T\hat{\Sigma}^{-1}\hat{\mu}_i - \frac{1}{2}\hat{\mu}_i^T\hat{\Sigma}^{-1}\boldsymbol{x} + \log(p(\omega_i))$$

- This classifier is *linear*:
  the linear normal density-based classifier.

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The two-class case (2)

- Define the discriminant $f(\boldsymbol{x}) = p(\omega_1|\boldsymbol{x}) - p(\omega_2|\boldsymbol{x}) > 0$
- We get $f(\boldsymbol{x}) = \boldsymbol{w}^T \boldsymbol{x} + w_0$

with $\boldsymbol{w} = \hat{\Sigma}^{-1}(\hat{\mu}_1 - \hat{\mu}_2)$

$$w_0 = \frac{1}{2}\hat{\mu}_2^T \hat{\Sigma}^{-1} \hat{\mu}_2 - \frac{1}{2}\hat{\mu}_1^T \hat{\Sigma}^{-1} \hat{\mu}_1 + \log \frac{p(\omega_1)}{p(\omega_2)}$$

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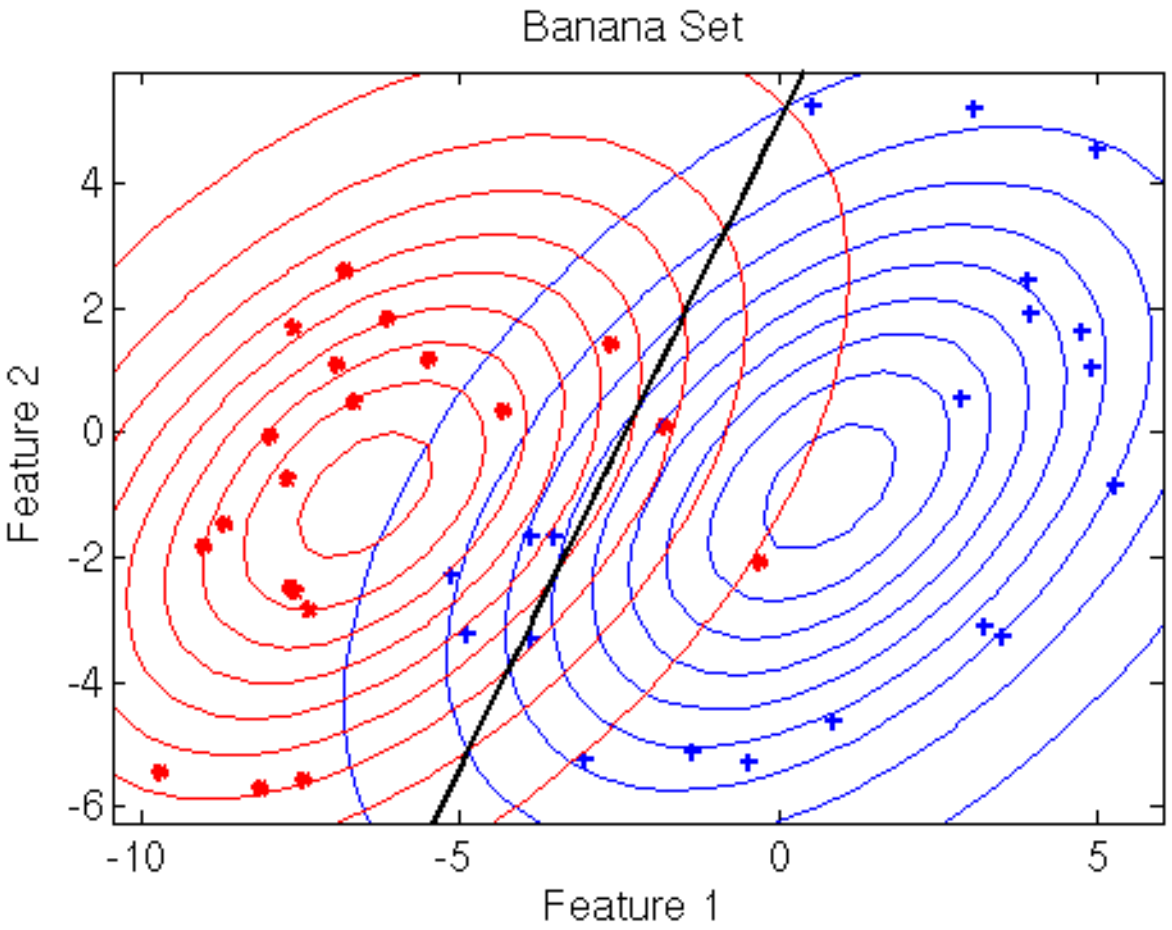
Linear classifier on banana data



No estimated full covariance matrix

- In some cases even the averaged covariance matrix is too much to estimate
- Assume that all features have the same variance, and are uncorrelated:

$$\hat{\Sigma} = \sigma^2 I$$

- Then it becomes even simpler:

$$g_i(\mathbf{x}) = -\frac{1}{2\hat{\sigma}^2}(\hat{\mu}_i^T \hat{\mu}_i - \hat{\mu}_i^T \mathbf{x}) + \log(p(\omega_i))$$

Nearest mean classifier

- Define the discriminant: $f(\boldsymbol{x}) = p(\omega_1|\boldsymbol{x}) - p(\omega_2|\boldsymbol{x}) > 0$
- We get $f(\boldsymbol{x}) = \boldsymbol{w}^T \boldsymbol{x} + w_0$

with $\boldsymbol{w} = \hat{\mu}_1 - \hat{\mu}_2$

$$w_0 = \frac{1}{2}\hat{\mu}_2^T \hat{\mu}_2 - \frac{1}{2}\hat{\mu}_1^T \hat{\mu}_1 + \hat{\sigma}^2 \log \frac{p(\omega_1)}{p(\omega_2)}$$

- Again a linear classifier, but it only uses the distance to the mean of each of the classes: *nearest mean* classifier

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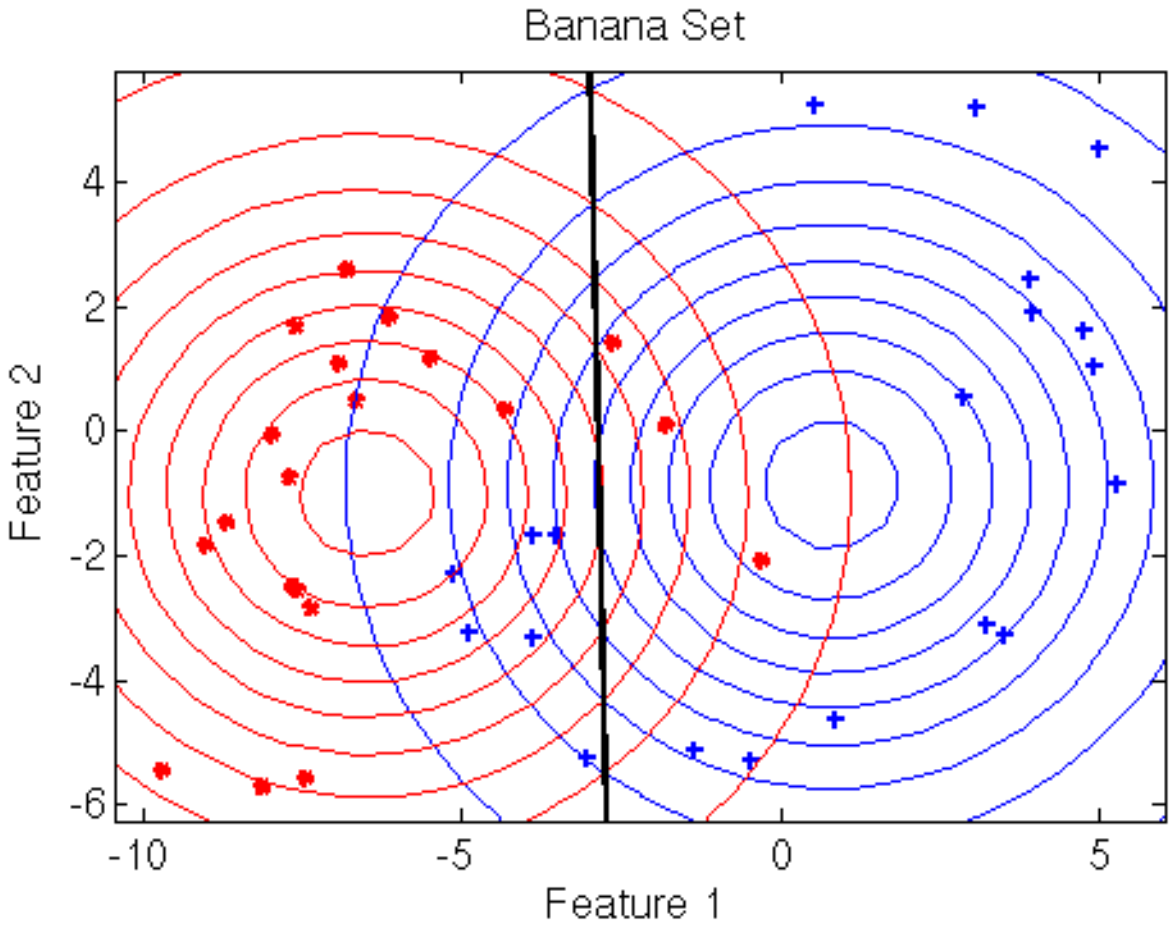
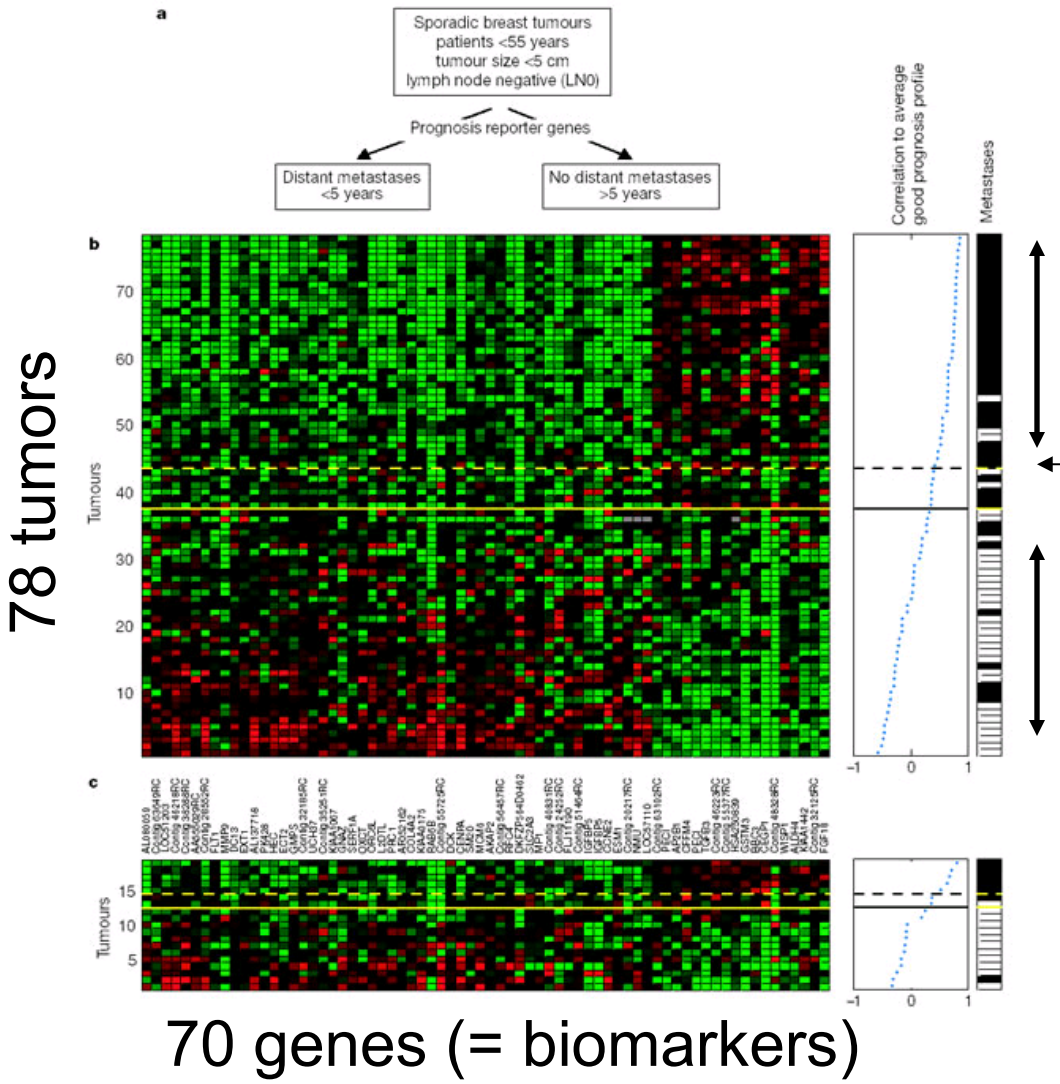
Nearest mean on banana data



Nearest mean on gene expression data



78 tumors

70 genes (= biomarkers)

Two classes:

no metastases > 5yr

metastases < 5yr

good prognosis

threshold

bad prognosis

Van 't Veer et al, Nature **415**, 530 (2002)

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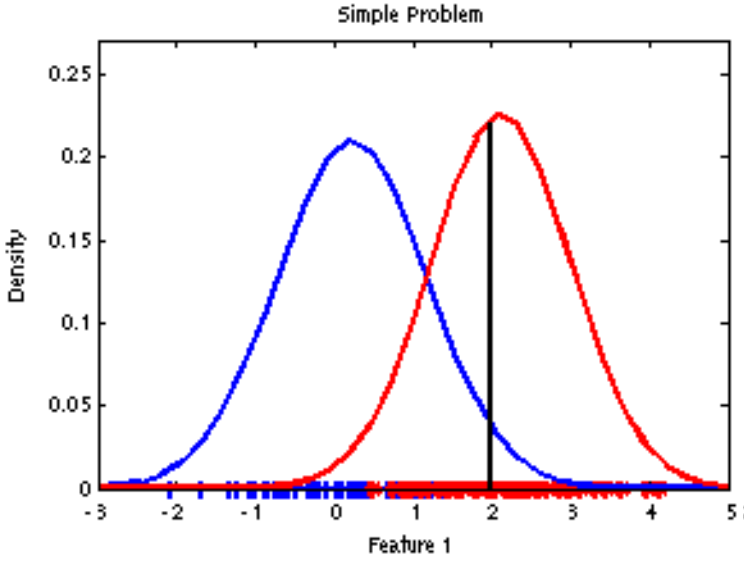
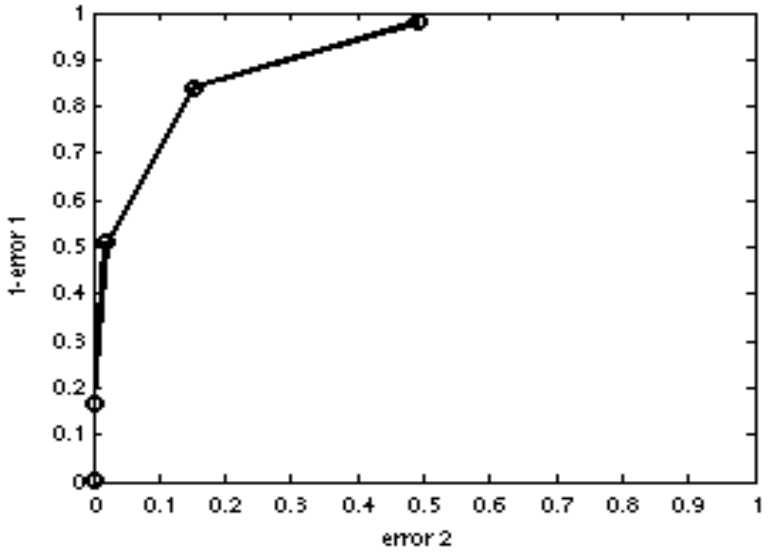
ROC curve

- Error as a function of the threshold gives an overview of all possible (cost/prior) scenarios: *receiver-operator characteristic curve*
- Classifier: any x left of the threshold belongs to the blue class, any x to the right to the red class





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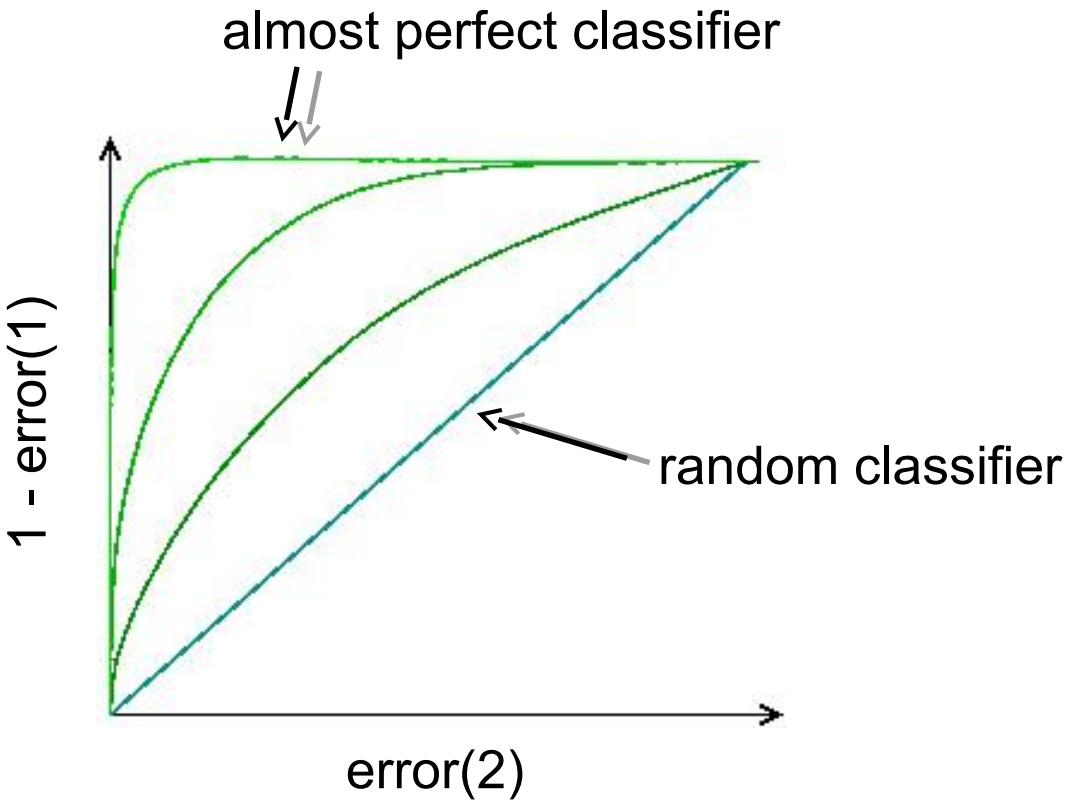
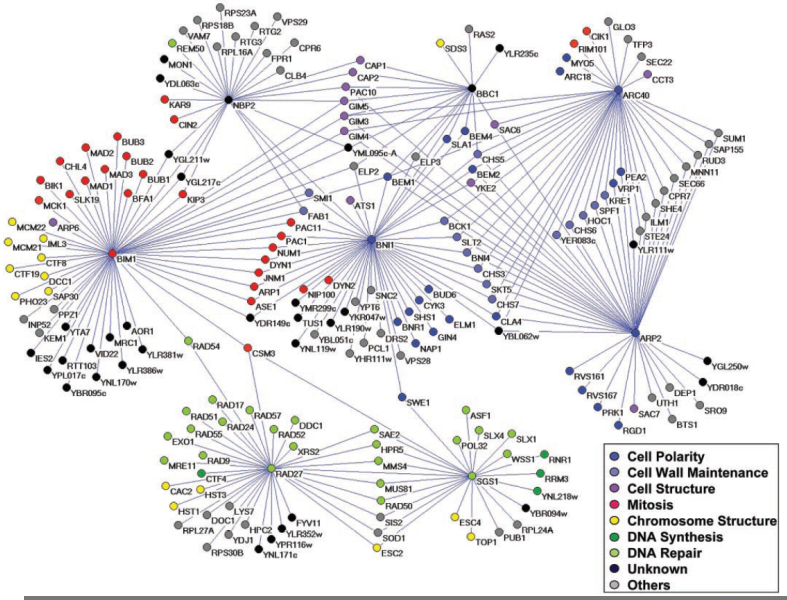
ROC curve (2)

- Different classifiers have different ROC curves

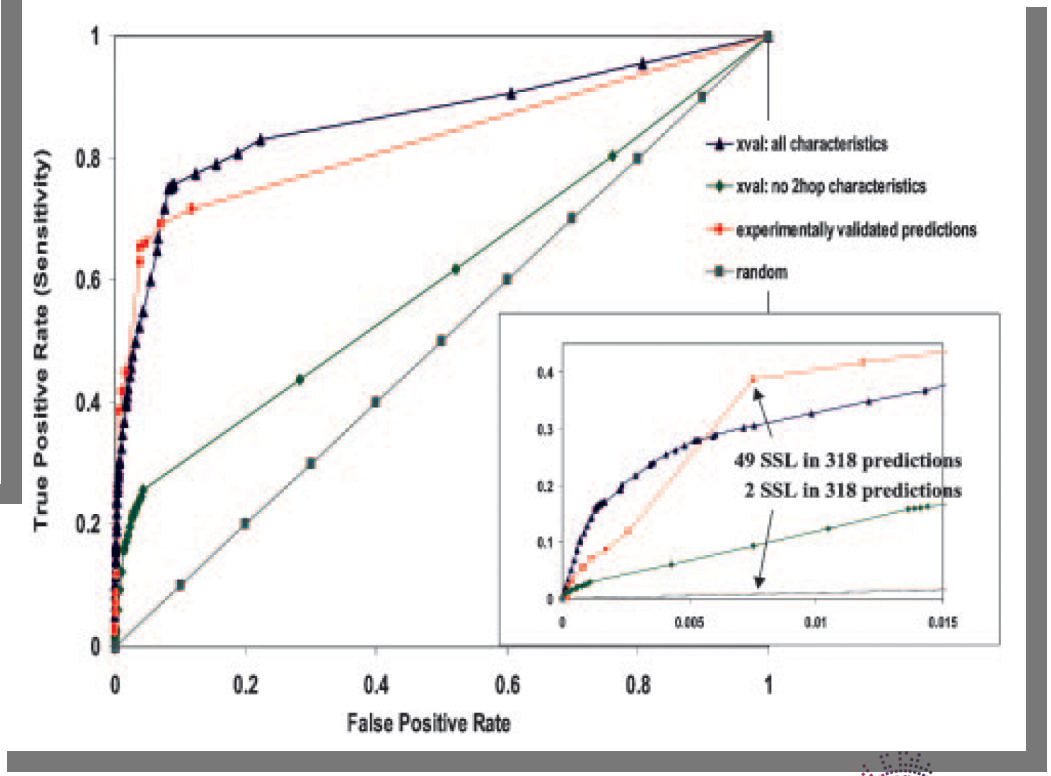


ROC curve (3)

- Example: prediction of synthetic genetic interactions (SGAs)



Wong et al., PNAS 2004



Recapitulation

- Using the Parzen density and nearest neighbor density we can derive the Parzen classifier and nearest neighbor classifier
- Using the plug-in Bayes' rule with a normal distribution for each of the classes gives different classifiers
  - Separate mean and covariance matrix per class gives the quadratic classifier
  - Separate mean, equal covariance matrix per class gives the linear classifier (see Fisher classifier, for two classes)
  - Separate mean, identity covariance matrix per class gives the nearest mean classifier
- By changing the thresholds a ROC curve is obtained, showing the error on both classes.

BioSB

Exercises 2.1-2.11

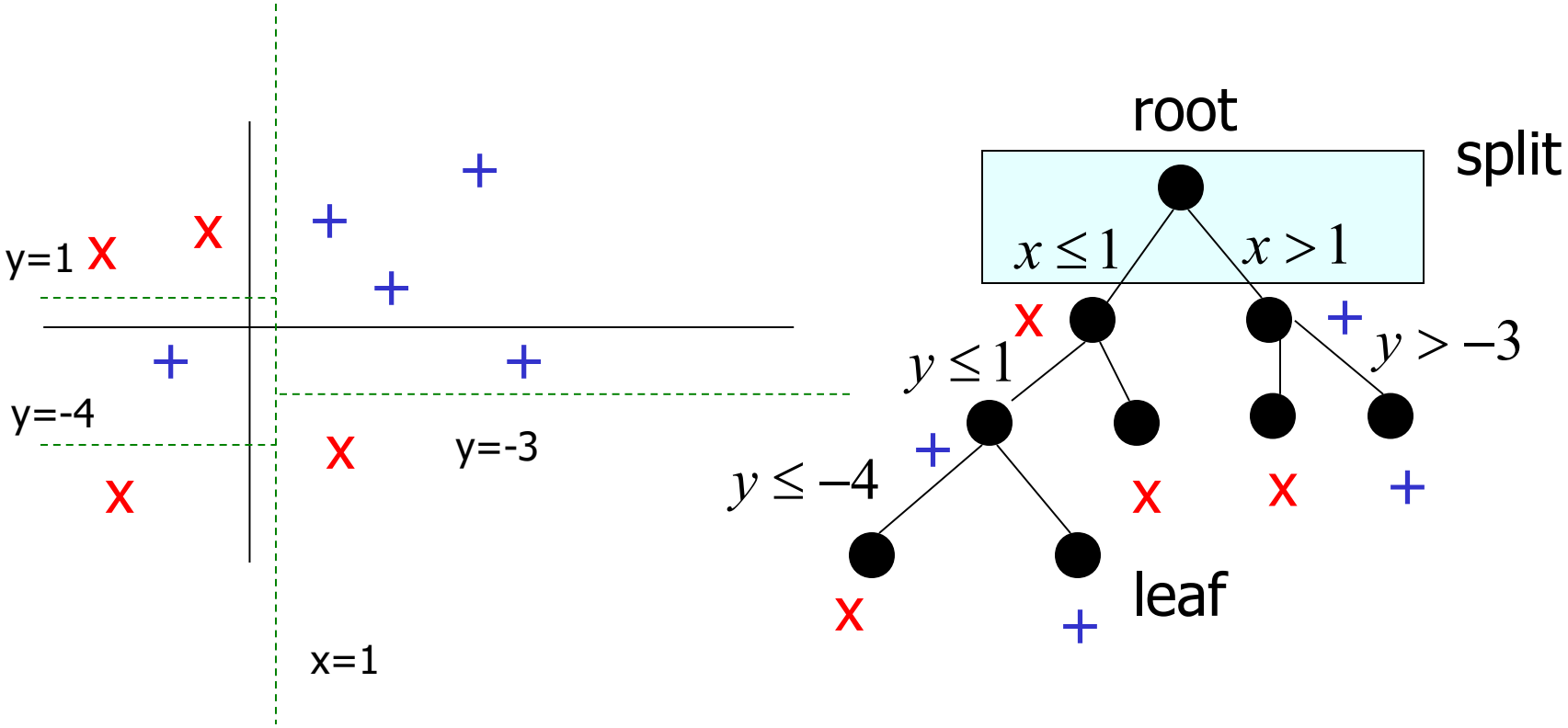
Tree-based models

- Until now: mainly linear and quadratic decision surfaces, often real data is more complex

- Classification trees
  - Feature selection
- Random forests
  - Ensemble of trees
  - Randomization
  - Bootstrapping
- More on Day 5: neural networks, support vector machines

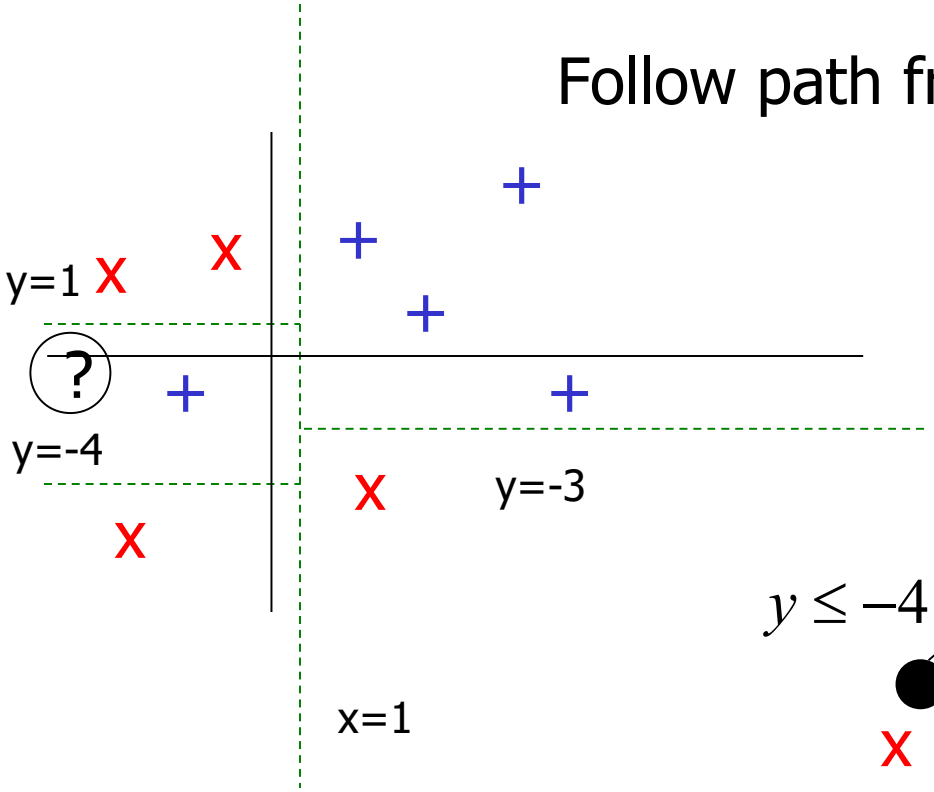
BioSB

Classification trees

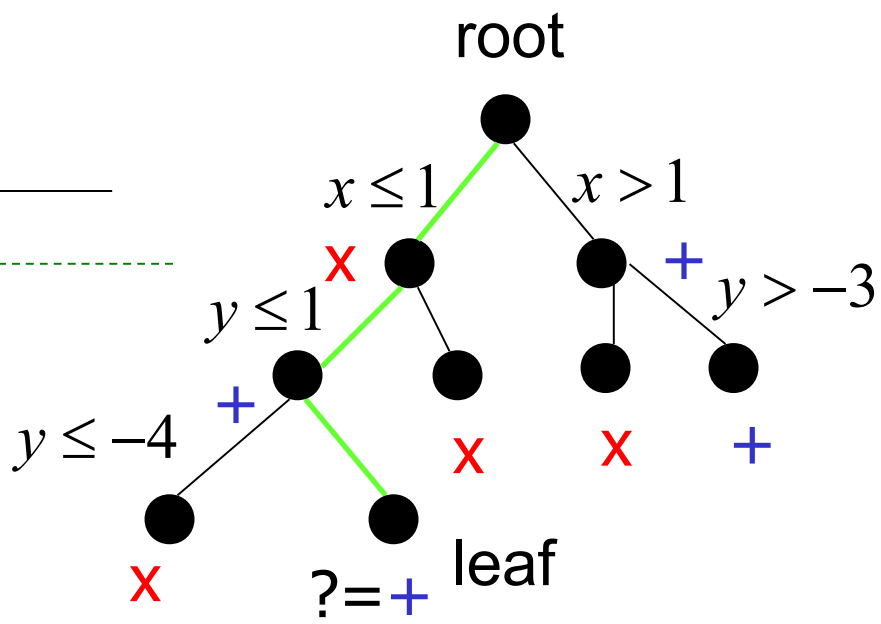


Build a tree of (binary) splits parallel to the axes in a greedy (=one by one) way.

Classification trees: new data

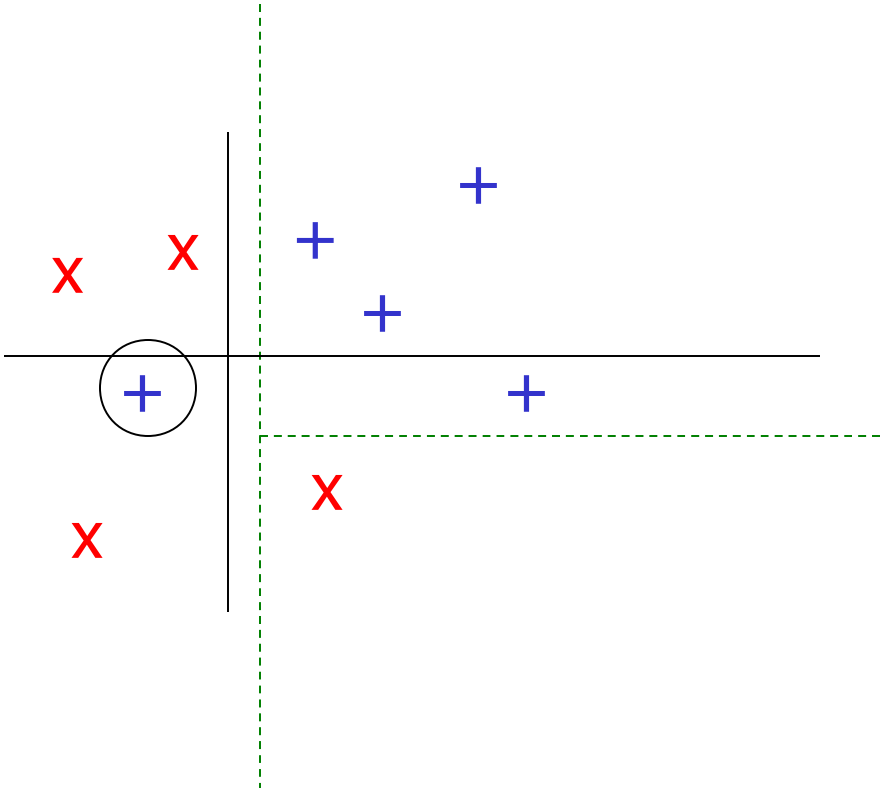


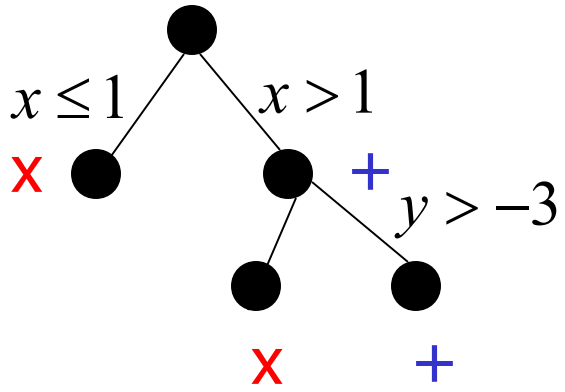
Follow path from root to one of the leaves



Can perfectly fit the data: overfitting

Classification trees: pruning





Allow errors on training data in order to reduce overfitting

Tree ingredients

Trees are constructed in a greedy way:
starting with an empty tree and adding splits one by one
(and never coming back on a decision taken)

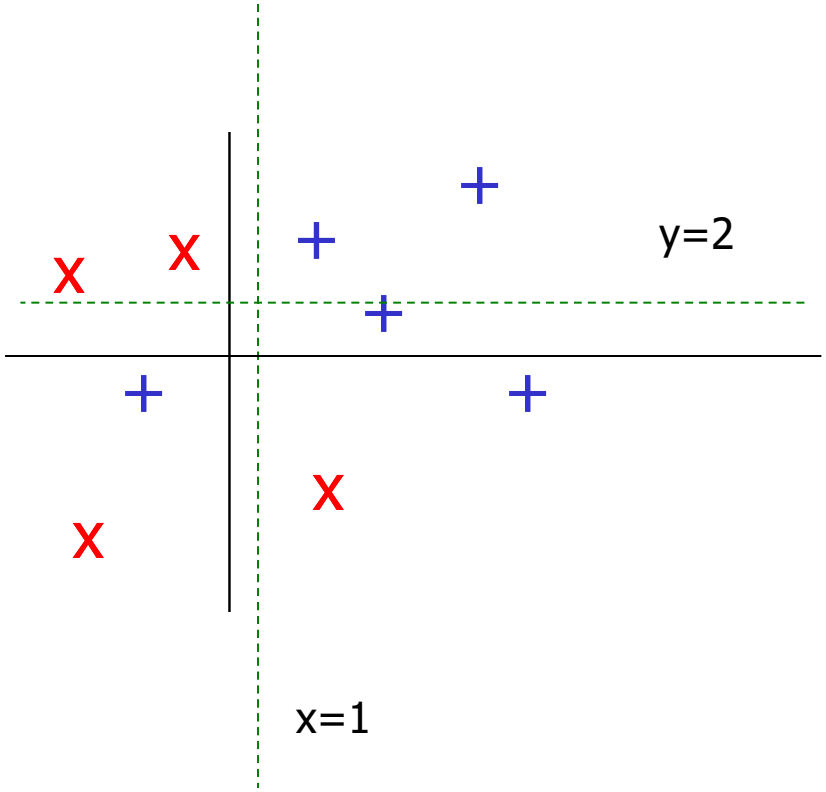
Main questions:

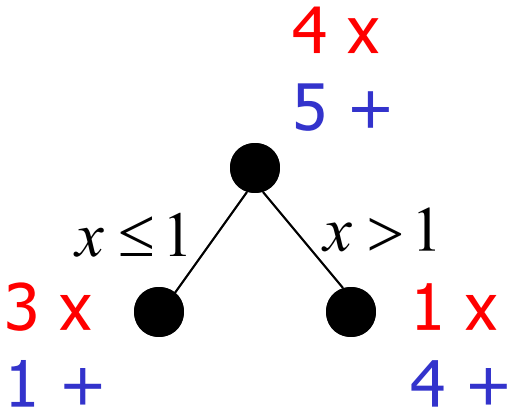
- How to choose a split
- How to choose a final tree?
  - Amount of pruning

Rest: details (but might be important …)

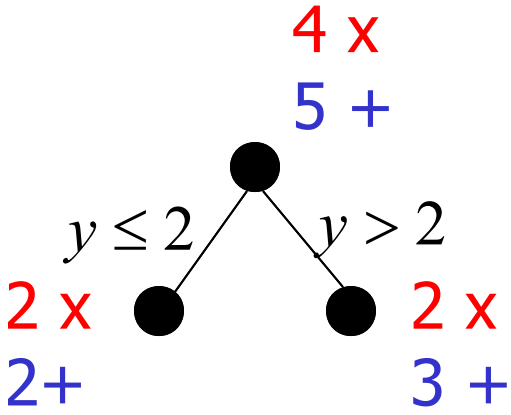
BioSB

How to choose a split?



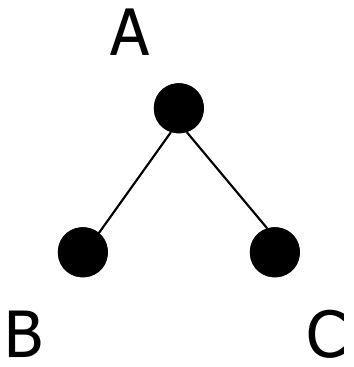


good



bad

How to choose a split? (2)

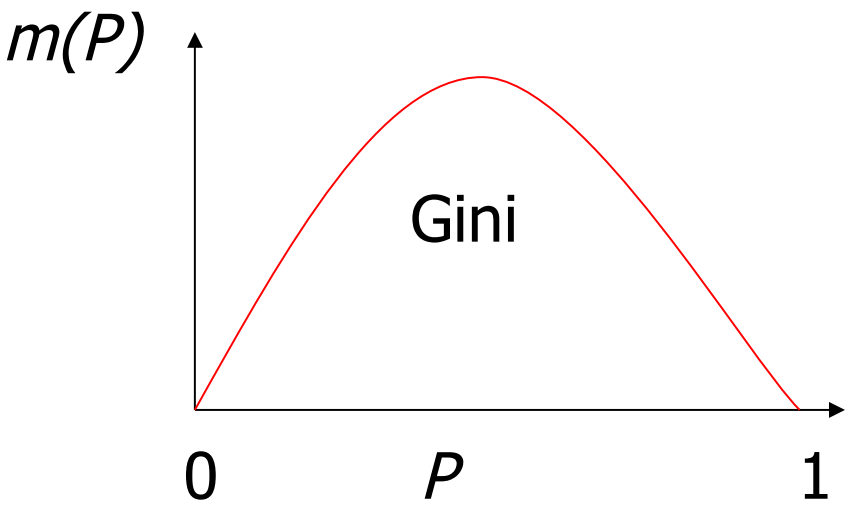


Good split at A:

- few x & many + in B, C

- many x & few + in B, C

Find some measure *m* that captures goodness



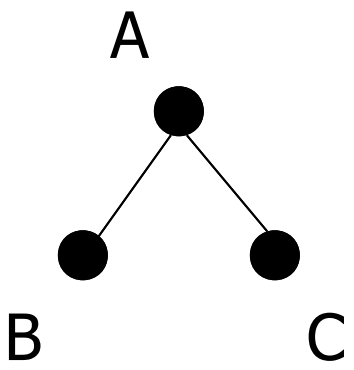
$m(0)=0$

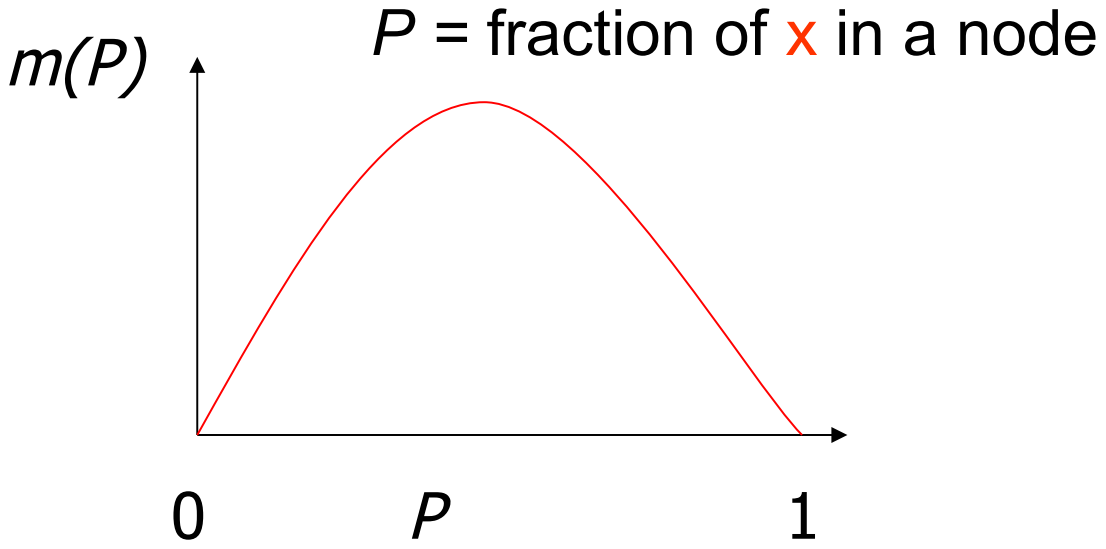
$m(1)=0$

$m(P)=P(1-P)$

P = fraction of x in a node

How to choose a split? (3)

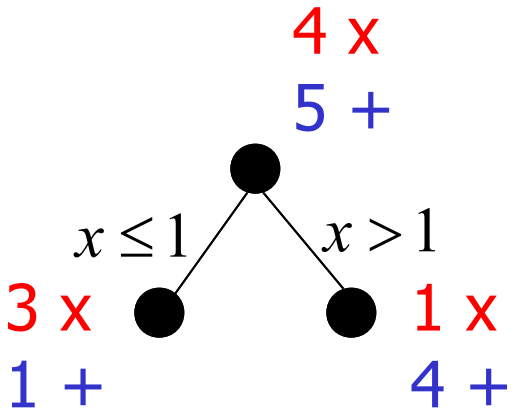




maximize $m(P_A) - P(B)m(P_B) - P(C)m(P_C)$

$P(X)$: determined by number of x and + at node X

How to choose a split? (4)



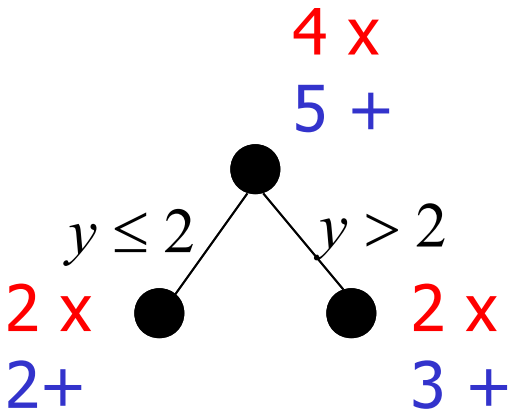
good

$$m(P_A) - P(B)m(P_B) - P(C)m(P_C)$$

$$\frac{4}{9}\frac{5}{9} - \frac{4}{9}\frac{3}{4}\frac{1}{4} - \frac{5}{9}\frac{1}{5}\frac{4}{5} =$$

0.075

maximum



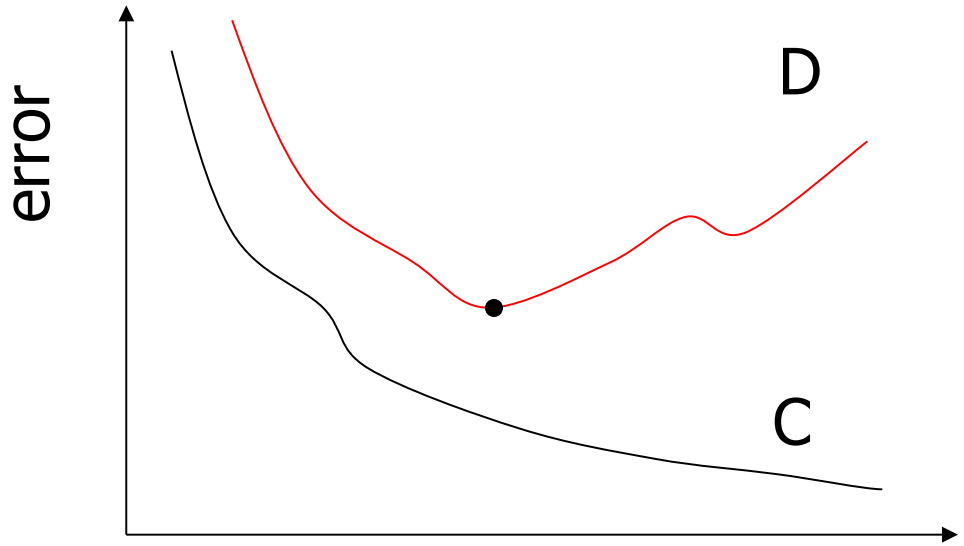
bad

$$\frac{4}{9}\frac{5}{9} - \frac{4}{9}\frac{2}{4}\frac{2}{4} - \frac{5}{9}\frac{2}{5}\frac{3}{5} =$$

0.0025

BioSB

Pruning: one step back

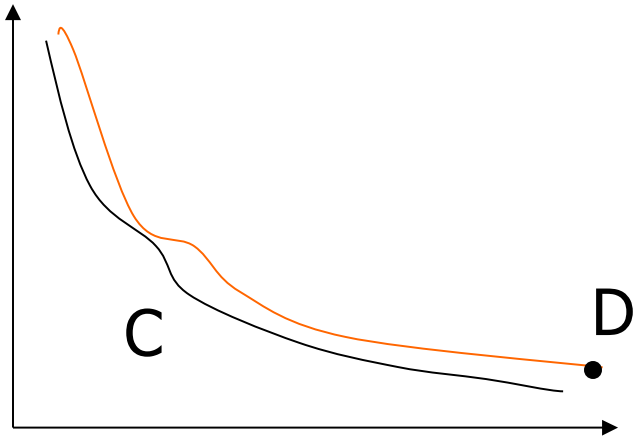


minimize: D = C + *k*(# of leaf nodes in the tree)

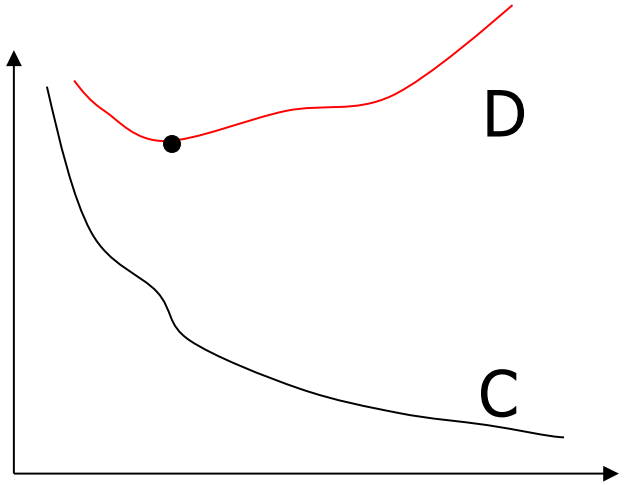
$0 \leq k$ *k*: complexity parameter

k penalizes big trees

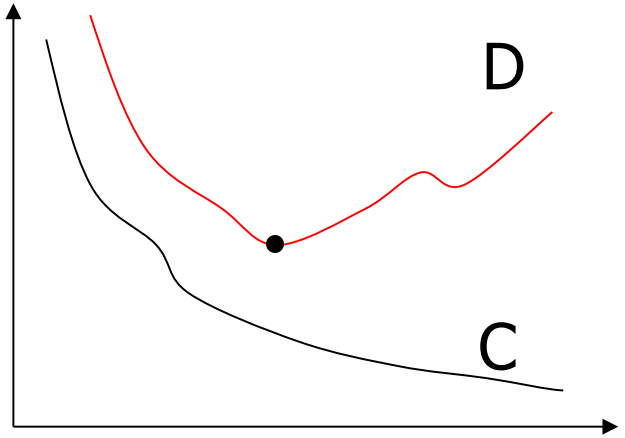
Pruning: one step back (2)



small *k*: big tree



large *k*: small tree



medium *k*: medium tree

BioSB

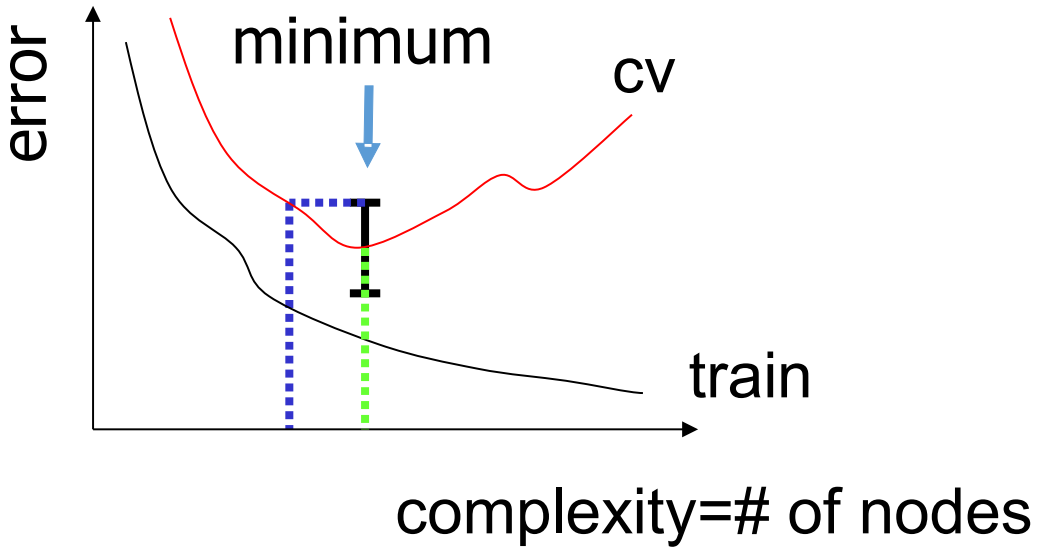
Pruning: CART

- Build a complete tree T
- With each subtree of T corresponds a choice of k

Cannot make choice of k on training set: overfitting

Optimal choice of k is made by cross-validation

Pruning: model selection



minimum

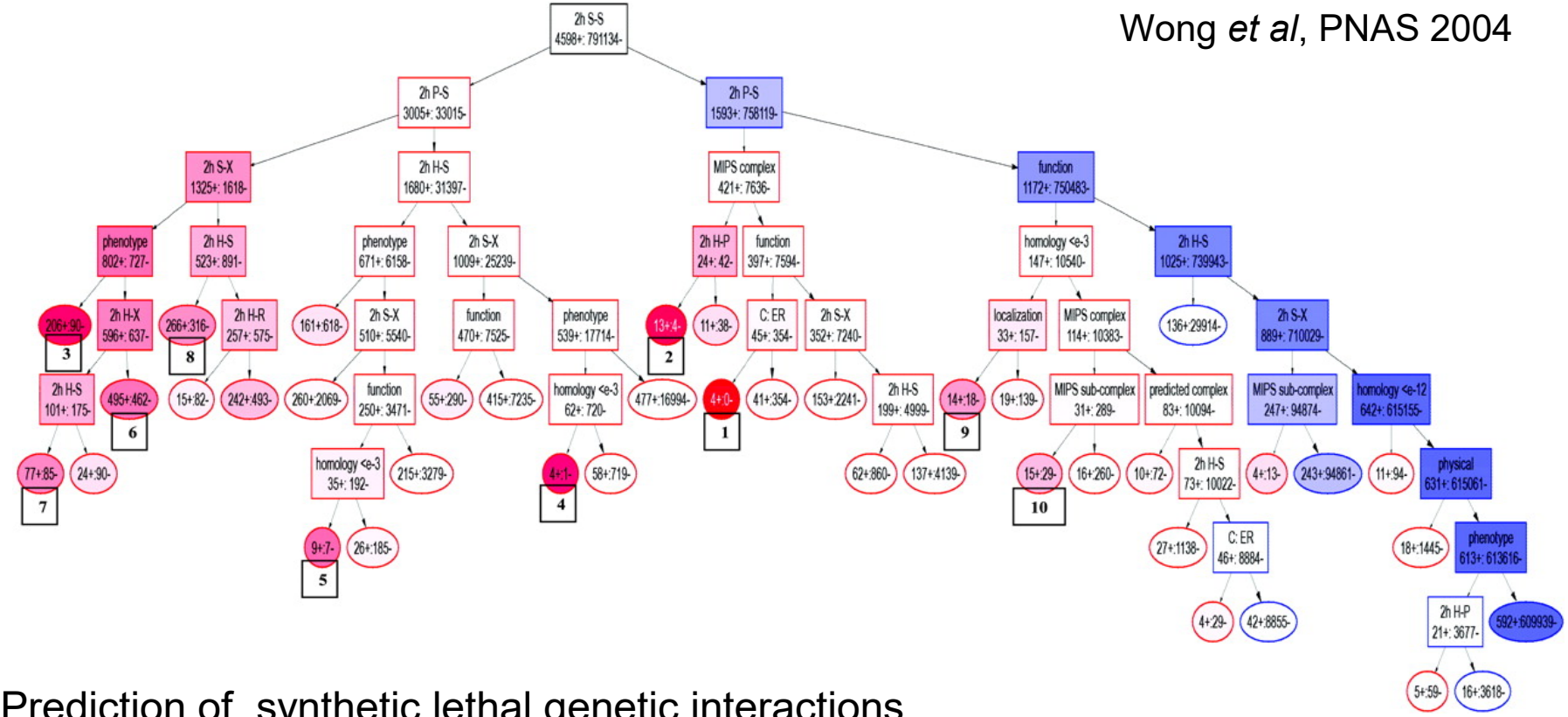
standard error (1-se)

10-fold cross-validation: mean +/- std. error

BioSB

Decision tree: application

Wong *et al*, PNAS 2004



- Prediction of synthetic lethal genetic interactions
- Integrate multiple types of data: localization, mRNA expression, physical interaction, protein function, and characteristics of network topology

BioSB

Advantages/disadvantages

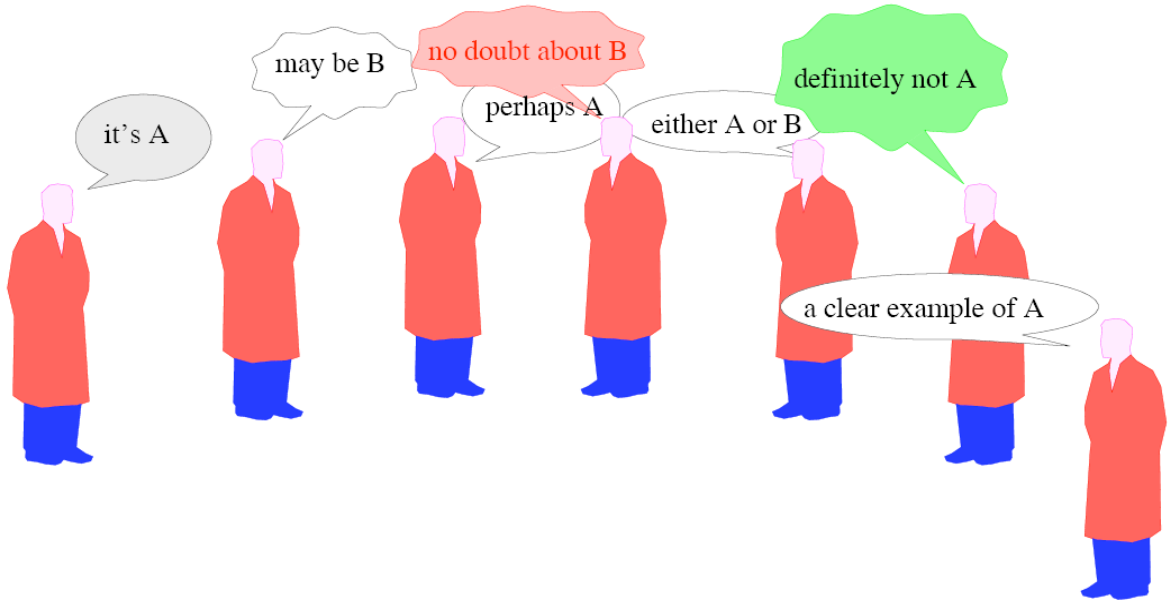
- simple and flexible classifier
- combination of discrete and continuous features
- feature selection (Day 3)
- interpretability

- hard splits
- splits are axis-aligned
- sensitive to small variations in data (high variance, Day 5)

BioSB

Classifier combination

- Idea: combine different classifiers and have them vote
- Design choices:
  - Identical or different?
    - Base classifiers, feature spaces, training sets, initialisations, etc.
  - Combination by a fixed rule or by another classifier?



BioSB

Example: random forests

- General overview: Day 4
- Specific example: random forest – an ensemble of decision trees

- Choices to be made:
  - Base classifiers: identical – decision trees
  - Feature spaces: for each node in each tree sample randomly *m* features
    - *m* << total number of features
  - Training sets: sampling with replacement (bootstrapping)
    - About two-third of the cases are used for training each tree
- Combination: majority vote

BioSB

Characteristics

- Out-of-bag error (oob) estimate:
  - Each tree can be tested on about one-third of the cases – the out-of-bag samples

- Variable importance:
  - For each tree: predict the class for oob cases and count the number of votes cast for the correct class
  - For each tree: randomly permute the values of variable *n* in the oob cases and count the number of votes cast for the correct class
  - Importance: rank (from high to low) based on average difference of these two scores

BioSB

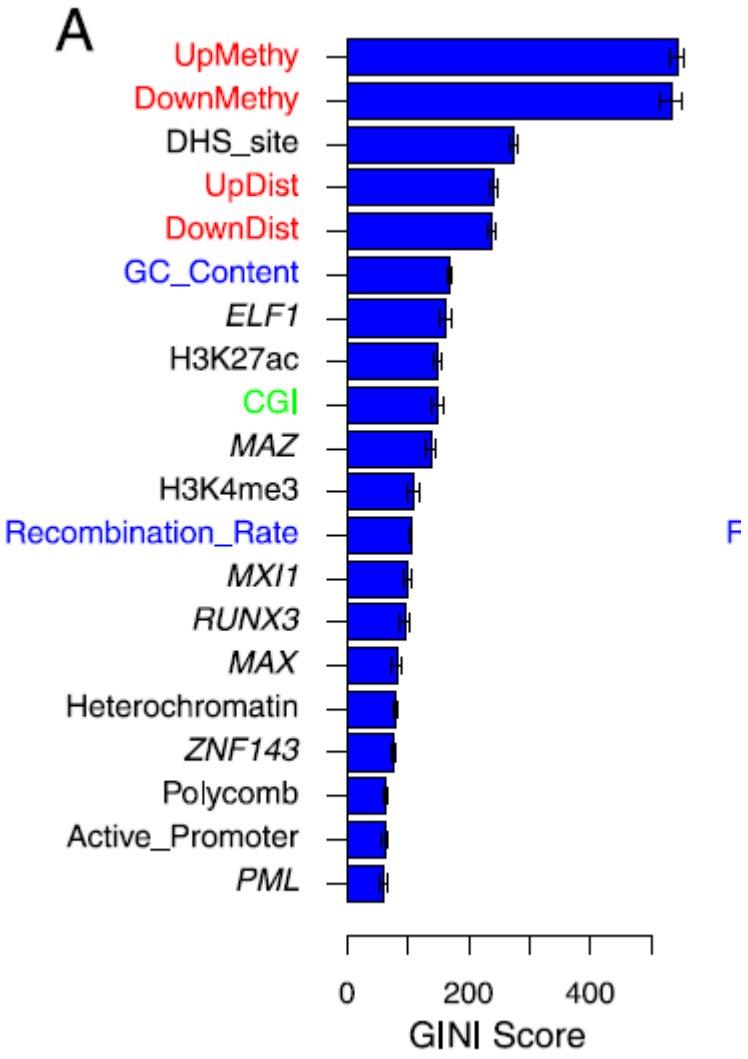
Some intuition

- Breiman *et al.*, Machine Learning (2001) paper
- Accuracy depends on two factors:
  - Correlation between any two trees in the forest. Decreasing correlation increases the forest accuracy: diversity
  - Accuracy of each individual tree (strength) in the forest. Increasing strength of individual trees increases the forest accuracy
- Trade-off:
  - Reducing *m* reduces correlation and strength
  - Increasing *m* increases correlation and strength
- Solution: somewhere in between is an *optimal* range of *m* - usually quite wide. Using the oob error rate a value of *m* in the range can be found

BioSB

Random forests: example

- Prediction of genome-wide DNA methylation
- Features:
  - Neighbors
  - Genomic position
  - DNA sequence properties
  - Cis-regulatory elements
- Random forest: feature selection



Zhang *et al.*, Genome Biology (2015)

Recapitulation

- Decision trees: simple and flexible classifier
  - Incorporates feature selection
  - Interpretable
  - Hard, axis-aligned splits
  - Pruning is essential to avoid overfitting
- Random forest: example of ensemble method
  - Ensemble of decision trees
  - Variation between members introduced via randomness
  - When number of features is large and percentage of truly informative features is small (gene expression-based diagnostics): performance tends to decline significantly

BioSB

Exercises 2.12-2.13

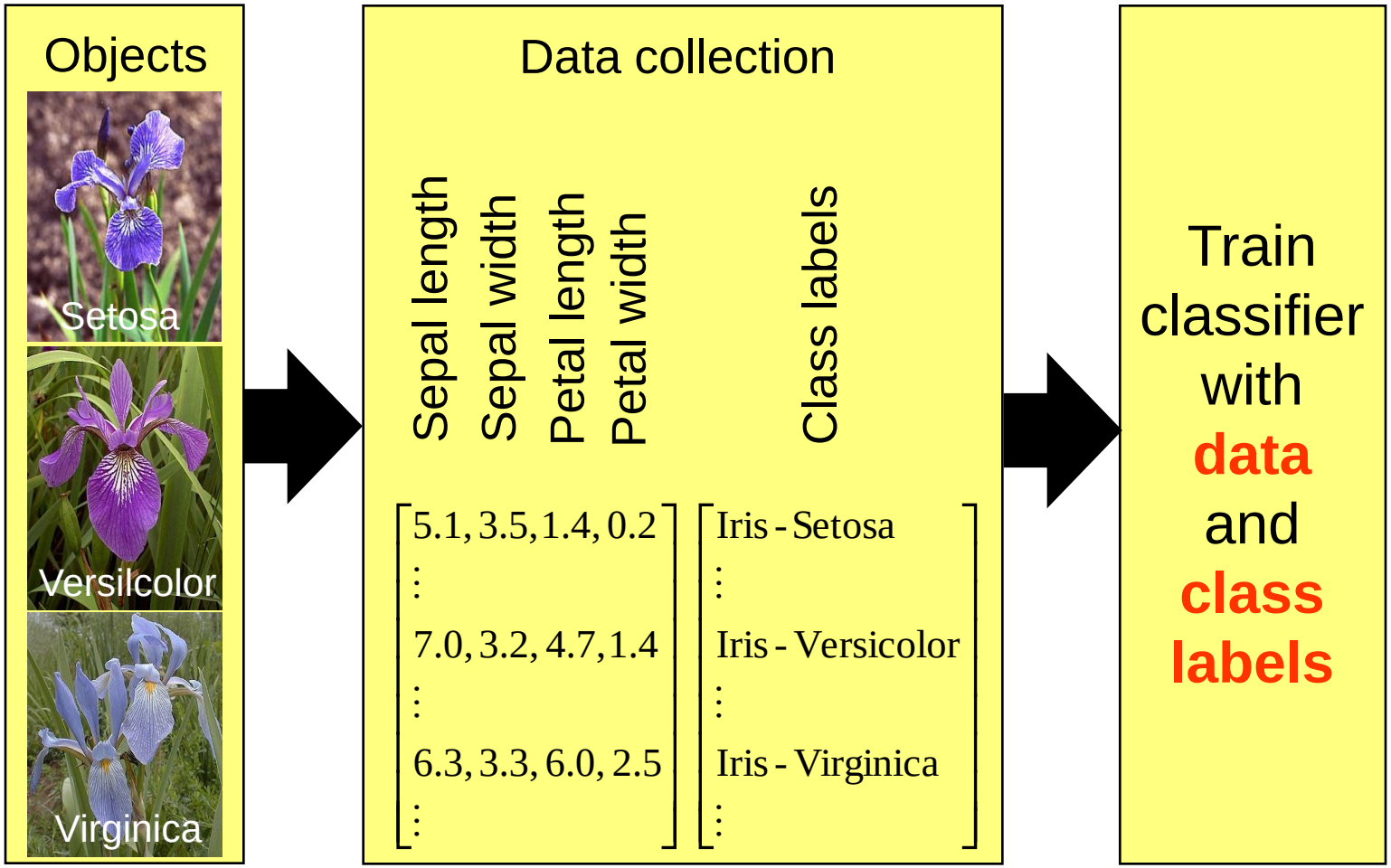
Clustering

- Supervised vs. unsupervised learning

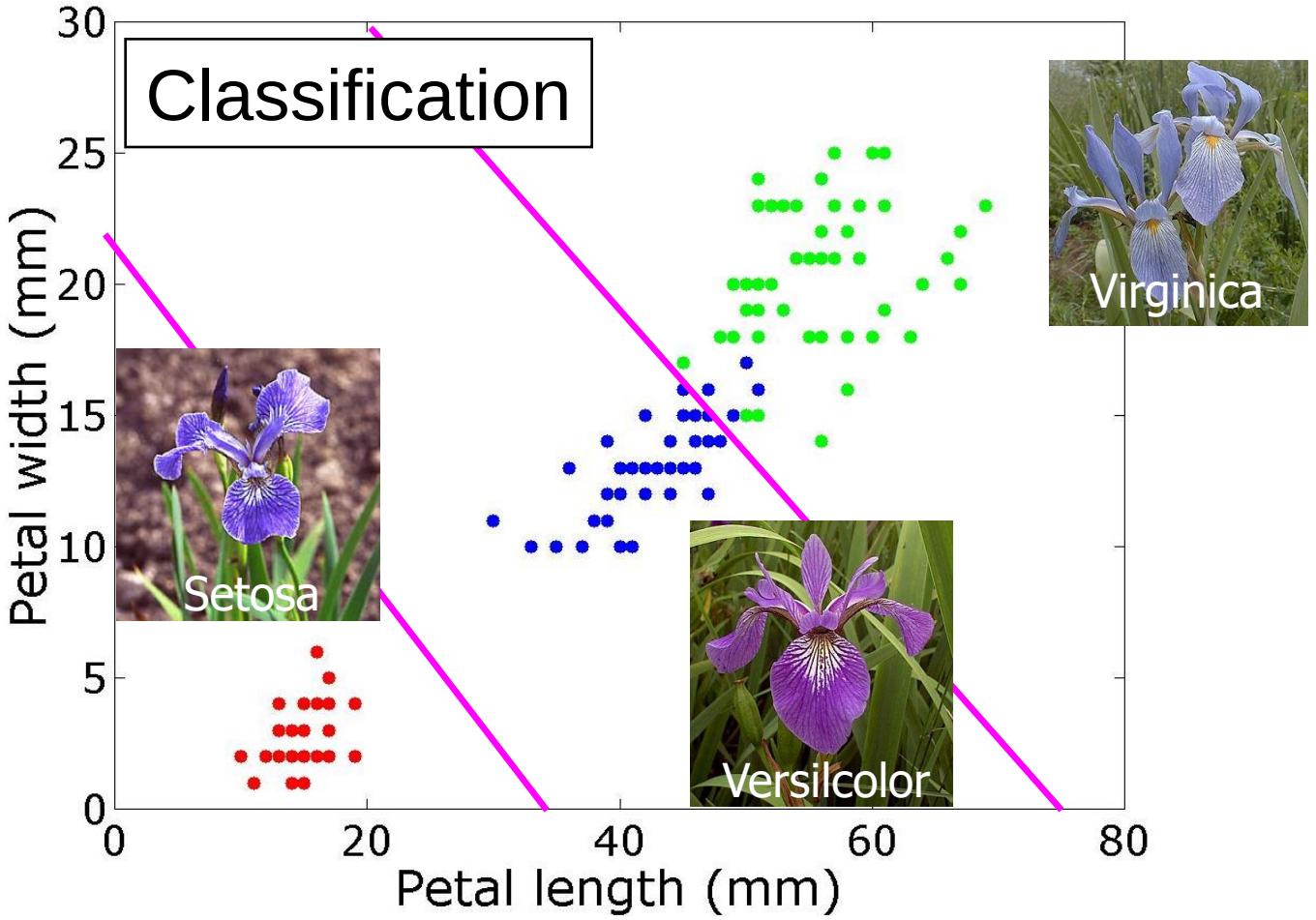
- Hierarchical clustering
- Sum-of-squares clustering (k-means)
- Cluster validation
- Mixtures-of-Gaussians clustering (EM algorithm)

BioSB

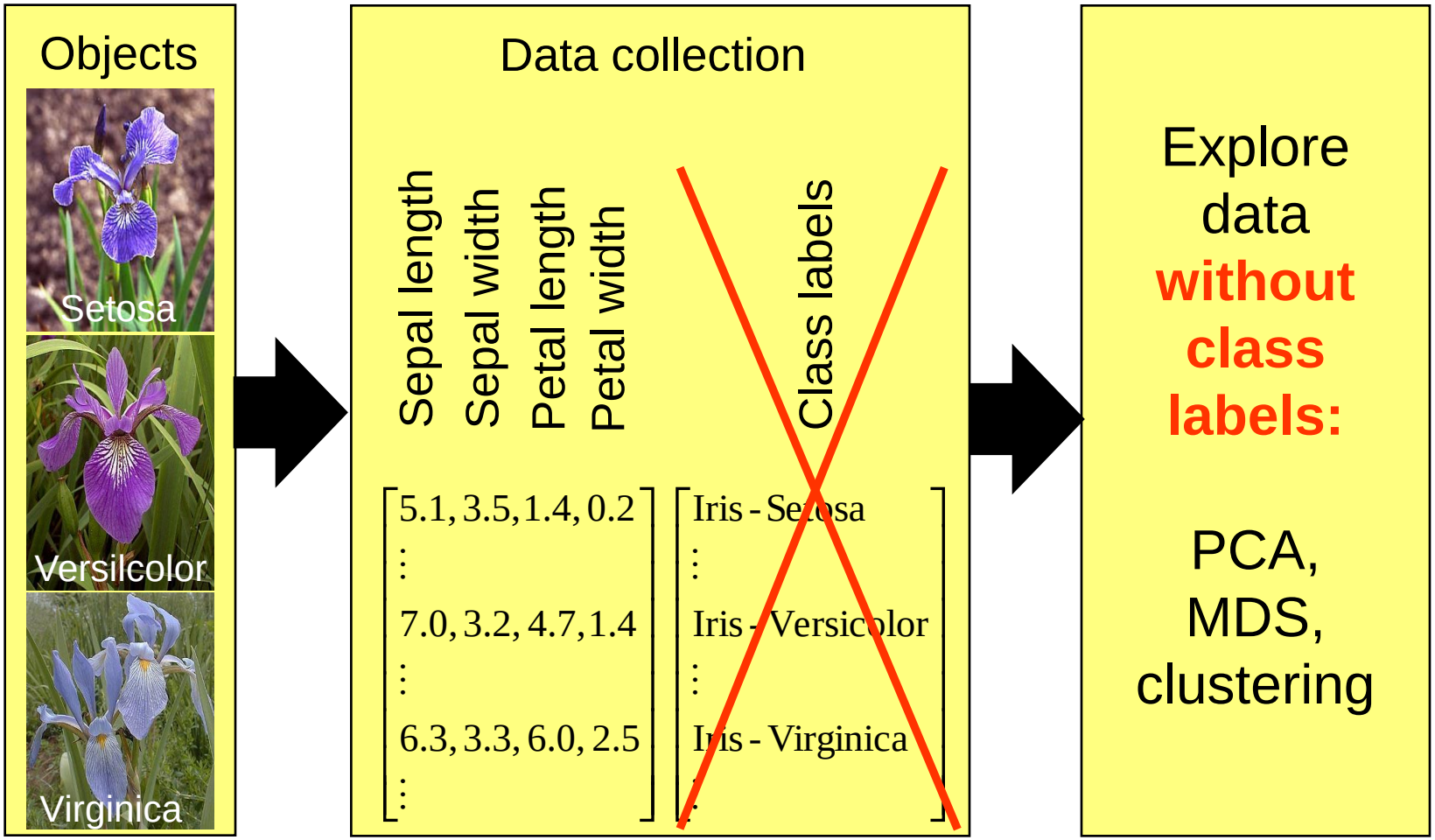
Supervised learning



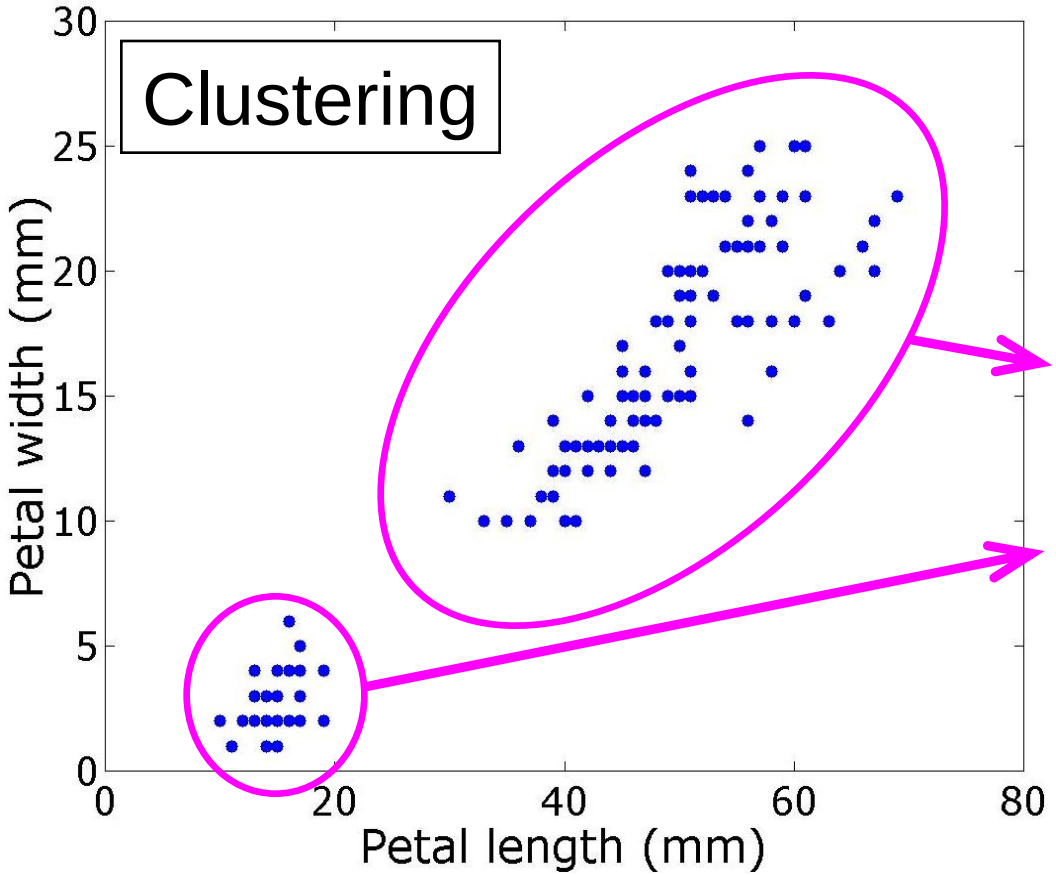
Supervised learning (2)



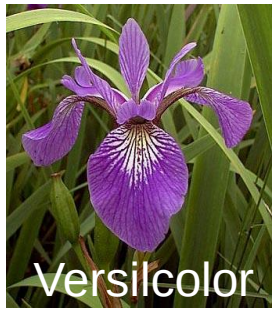
Unsupervised learning



Unsupervised learning (2)

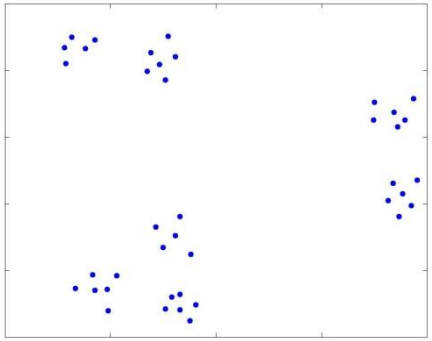


?

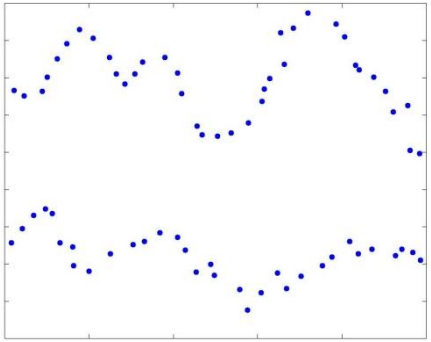


BioSB

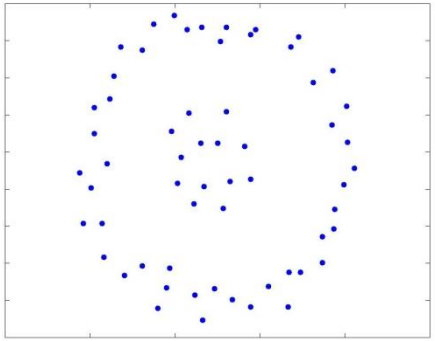
What is a cluster?



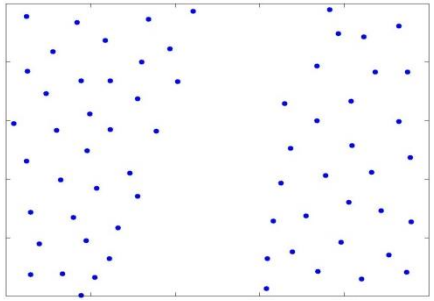
Shape: compact, convex
Separation: large



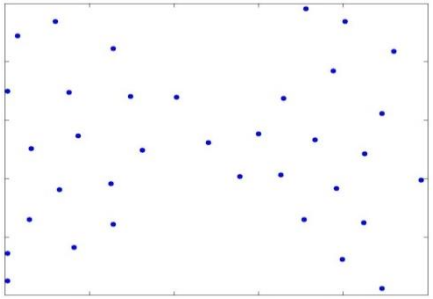
Shape: strings
Separation: large?



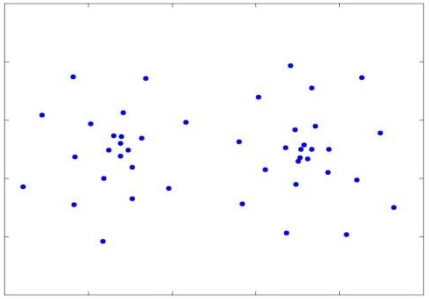
Shape: convex and circular
Separation: large?



Shape: ?
Separation: large?



Shape: loose, convex
Separation: small



Shape: loose, convex
Separation: small

BioSB

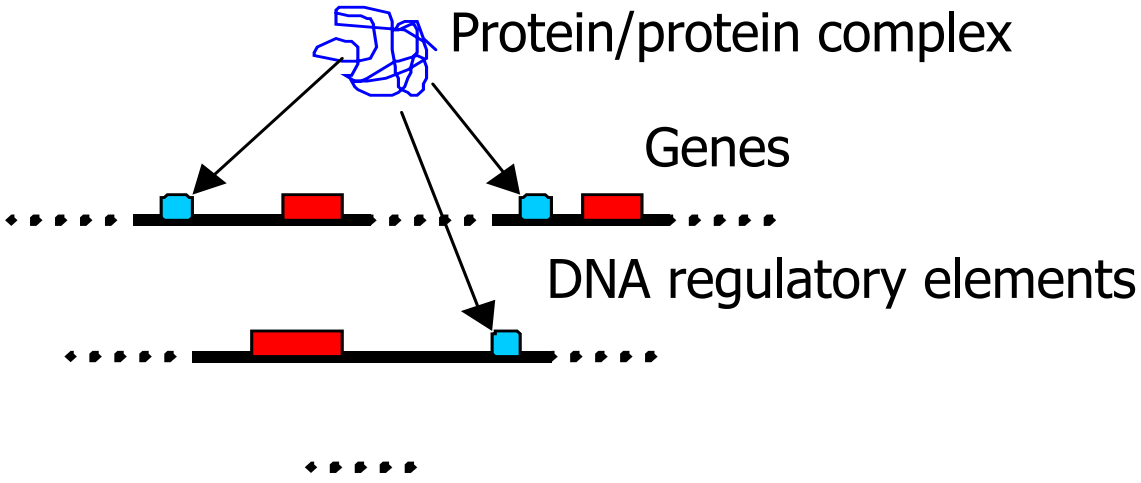
What is a cluster? (2)

- Clustering: finding natural groups in data...
  - which themselves are far apart
  - in which objects are close together
- Define what is “far apart” and “close together”:
  - Need a distance measure or dissimilarity measure
  - This measure should capture what we think is important for the grouping
  - The choice for a certain distance measure is often the most important choice in clustering!
- There is no such thing as *the objective clustering*

BioSB

What is a cluster in bioinformatics?

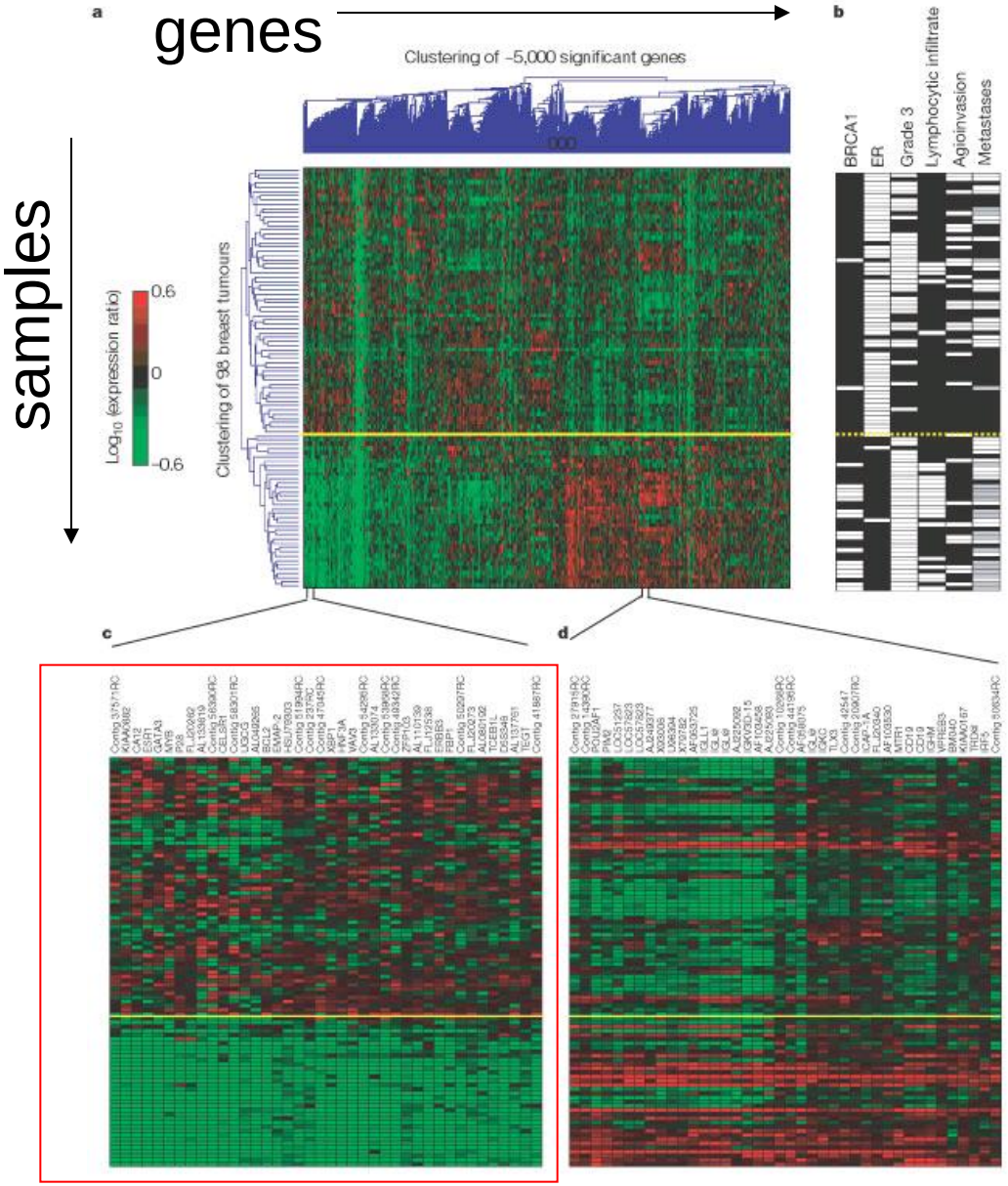
- Clustering gene expression data:
- Genes: similar ~ co-expression ~ co-regulation ~
  same pathway / same function



- Samples: similar ~ same type of tissue
- Used for discovery of new subclasses (*subtypes*) in tumors

BioSB

Example: genes (and samples)



negative

positive

histopathological data

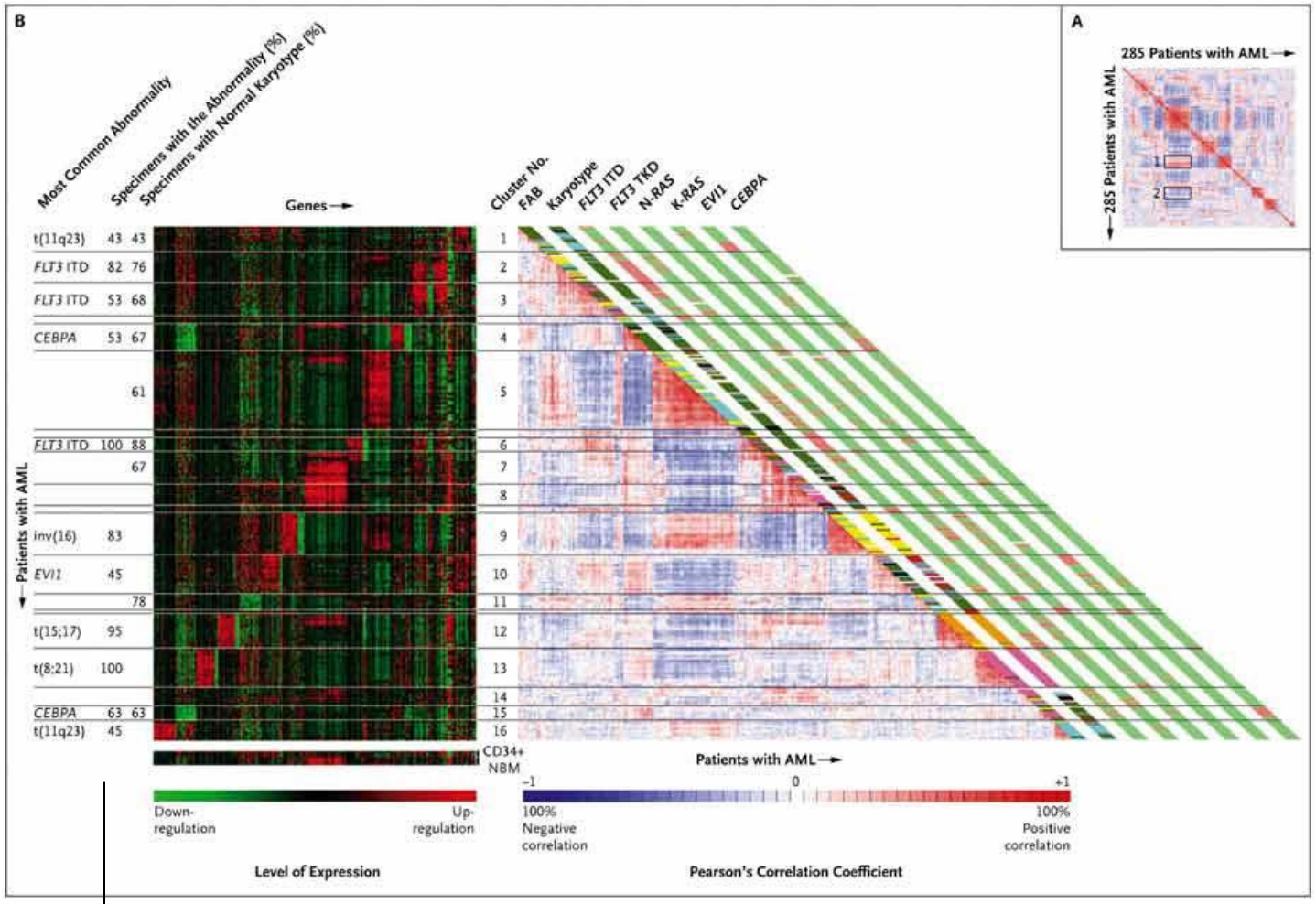
ER gene *(ESR1)* and genes co-regulated with ER, some of which are known ER target genes

Van 't Veer et al, Nature 415: 530-536 (2002)

BioSB

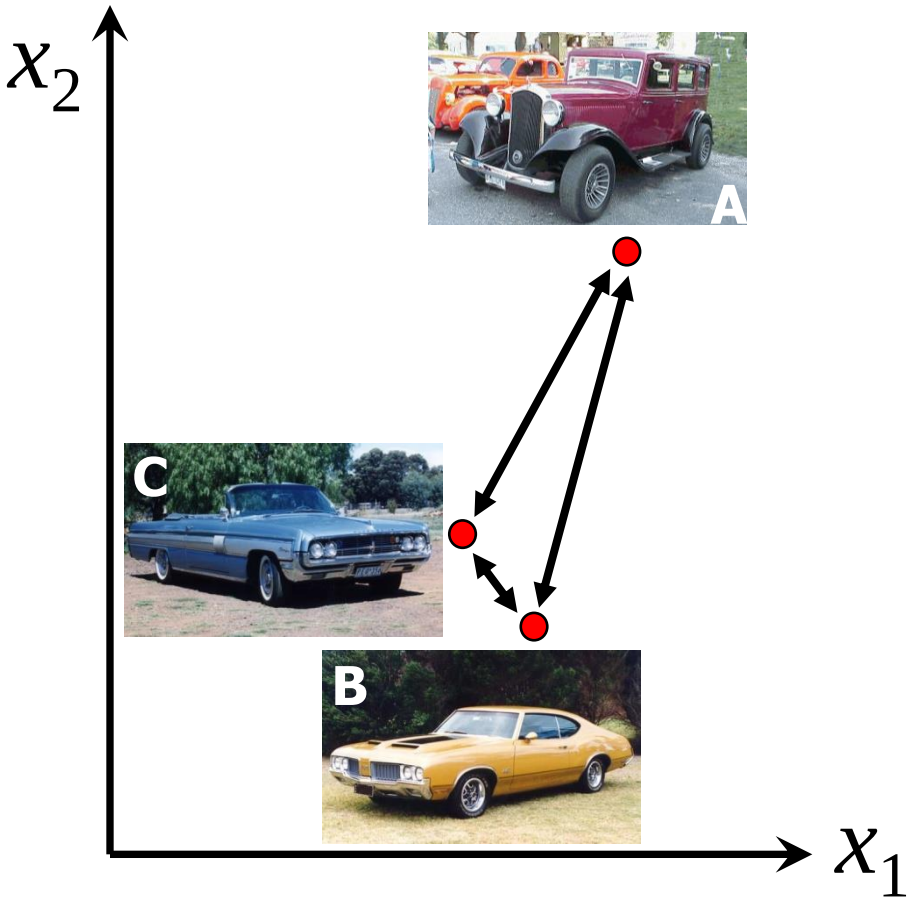
Example: samples

Valk et al, N Engl J Med. 2004 Apr 15;350(16):1617-28.



Identified 16 groups of patients with acute myeloid leukemia

Dissimilarity measures



$$\boldsymbol{D} = \begin{bmatrix} 0 & d(\mathbf{A},\mathbf{B}) & d(\mathbf{A},\mathbf{C}) \\ & 0 & d(\mathbf{B},\mathbf{C}) \\ & & 0 \end{bmatrix}$$

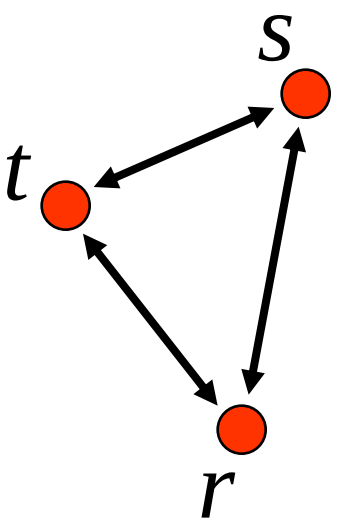
$$= \begin{bmatrix} 0 & 10 & 11 \\ & 0 & 2 \\ & & 0 \end{bmatrix}$$

BioSB

Dissimilarity measures (2)

- Let $d(r,s)$ be the dissimilarity between objects *r* and *s*
- Formally, dissimilarity measures should satisfy

$$d(r,s) \geq 0, \forall\, r,s$$
$$d(r,r) = 0, \forall\, r$$
$$d(r,s) = d(s,r), \forall\, r,s$$



- If in addition, the triangle inequality holds, the measure is a *metric*

$$d(r,t) + d(t,s) \geq d(r,s), \forall\, r,s,t$$

- Most often used: Euclidean distance (metric)

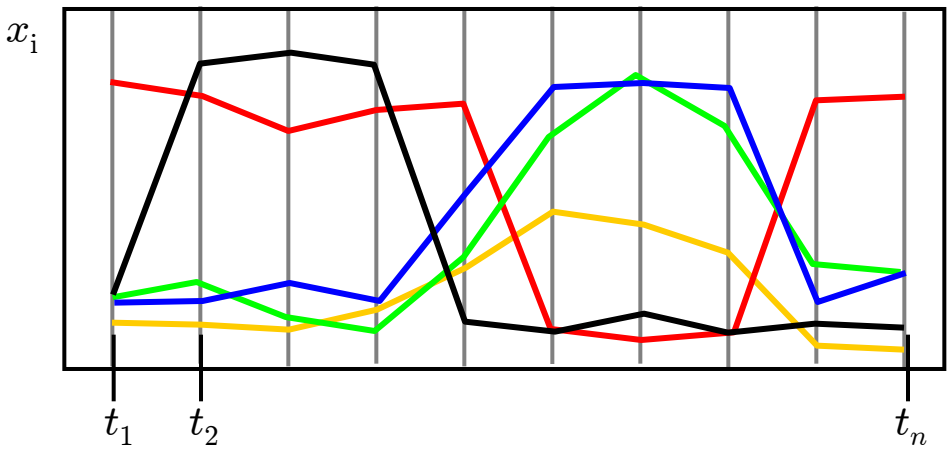
BioSB

Dissimilarity measures (3)

- Example: time series data

(squared) Euclidean distance

$$d(\mathbf{x}_i, \mathbf{x}_j) = \sum_{t=1}^{n} (x_{i,t} - x_{j,t})^2$$



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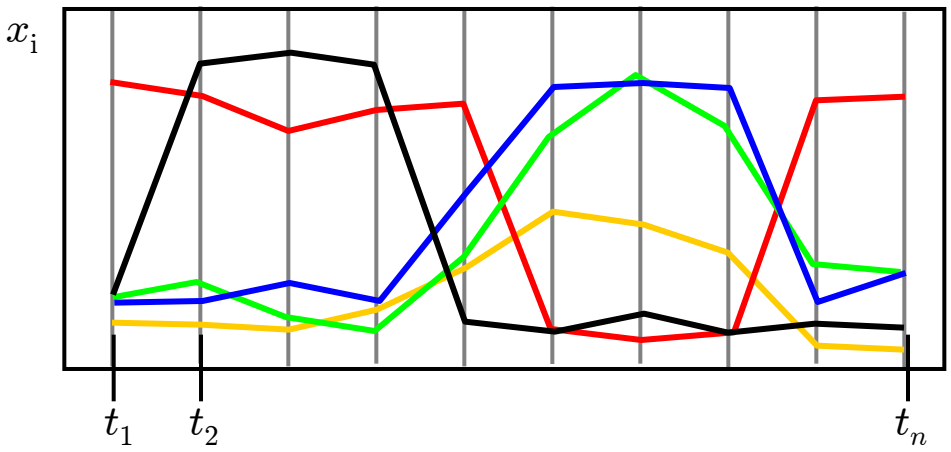
Dissimilarity measures (3)

- Example:
  time series data



Euclidean distance
match exact shape

$$d(\mathbf{x}_i, \mathbf{x}_j) = \sum_{t=1}^{n} (x_{i,t} - x_{j,t})^2$$

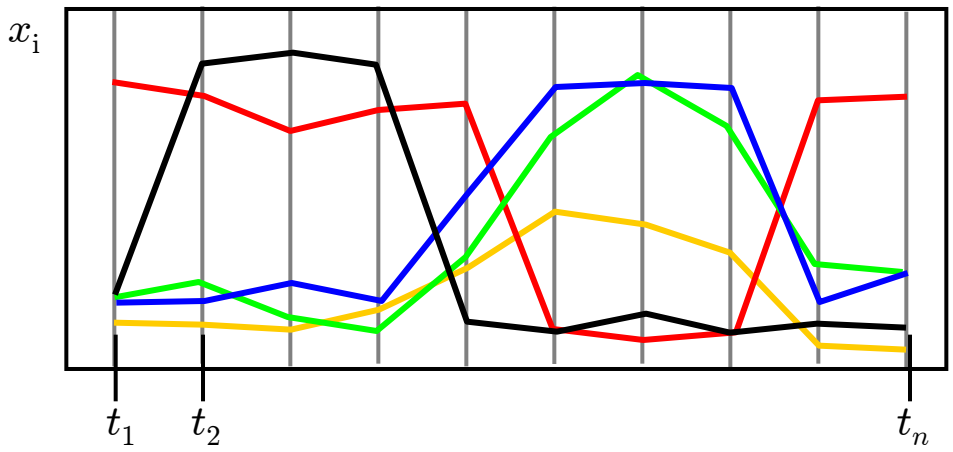
d(● , ●) < d(● , ●)
d(● , ●) << d(● , ●)
d(● , ●) << d(● , ●)

Dissimilarity measures (3)

- Example: time series data

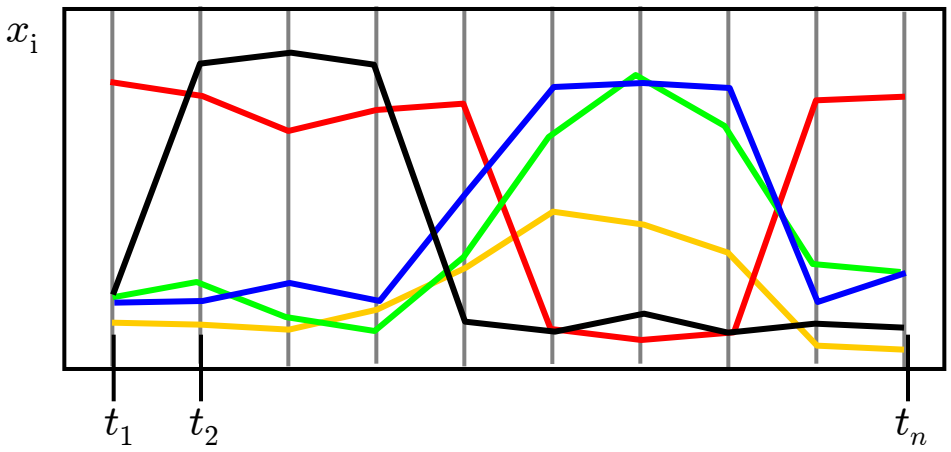
Euclidean distance
match exact shape

$$d(\mathbf{x}_i, \mathbf{x}_j) = \sum_{t=1}^{n} (x_{i,t} - x_{j,t})^2$$



Dissimilarity measures (3)

- Example: time series data



Euclidean distance
match exact shape

$$d(\mathbf{x}_i, \mathbf{x}_j) = \sum_{t=1}^{n} (x_{i,t} - x_{j,t})^2$$

d(● , ●) < d(● , ●)
d(● , ●) << d(● , ●)
d(● , ●) << d(● , ●)

Pearson correlation
ignore amplitude

$$\rho_{ij} = \sum_{t=1}^{n} (x_{i,t} - \mu_i)(x_{j,t} - \mu_j) \Big/ \sigma_i \sigma_j$$

$1 - \rho_{ij}$

d(● , ●) ≈ d(● , ●)
d(● , ●) << d(● , ●)
d(● , ●) << d(● , ●)

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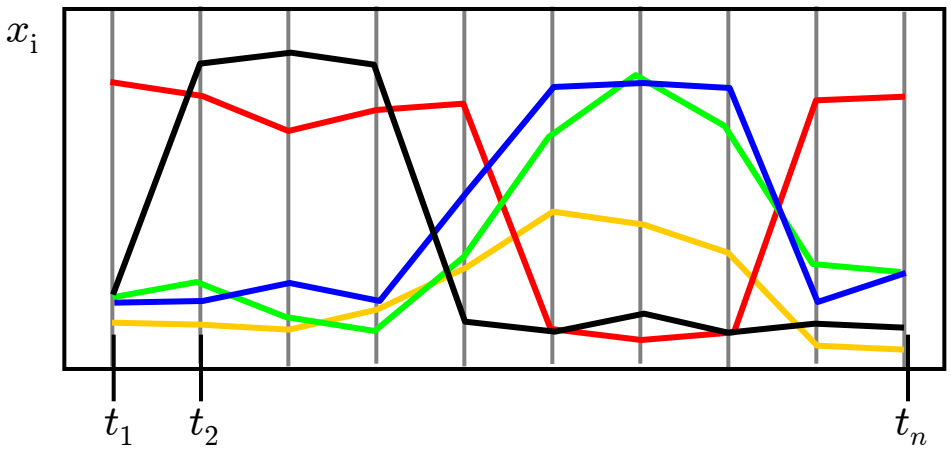
Dissimilarity measures (3)

- Example: time series data



Euclidean distance
match exact shape

$$d(\mathbf{x}_i, \mathbf{x}_j) = \sum_{t=1}^{n} (x_{i,t} - x_{j,t})^2$$

d(● , ●) < d(● , ●)
d(● , ●) << d(● , ●)
d(● , ●) << d(● , ●)

Pearson correlation
ignore amplitude

$$\rho_{ij} = \sum_{t=1}^{n} (x_{i,t} - \mu_i)(x_{j,t} - \mu_j) \Big/ \sigma_i \sigma_j$$

$$1 - \rho_{ij}$$

d(● , ●) ≈ d(● , ●)
d(● , ●) << d(● , ●)
d(● , ●) << d(● , ●)

Absolute correlation
ignore amplitude & sign

$$1 - |\rho_{ij}|$$

d(● , ●) ≈ d(● , ●)
d(● , ●) ≈ d(● , ●)
d(● , ●) << d(● , ●)

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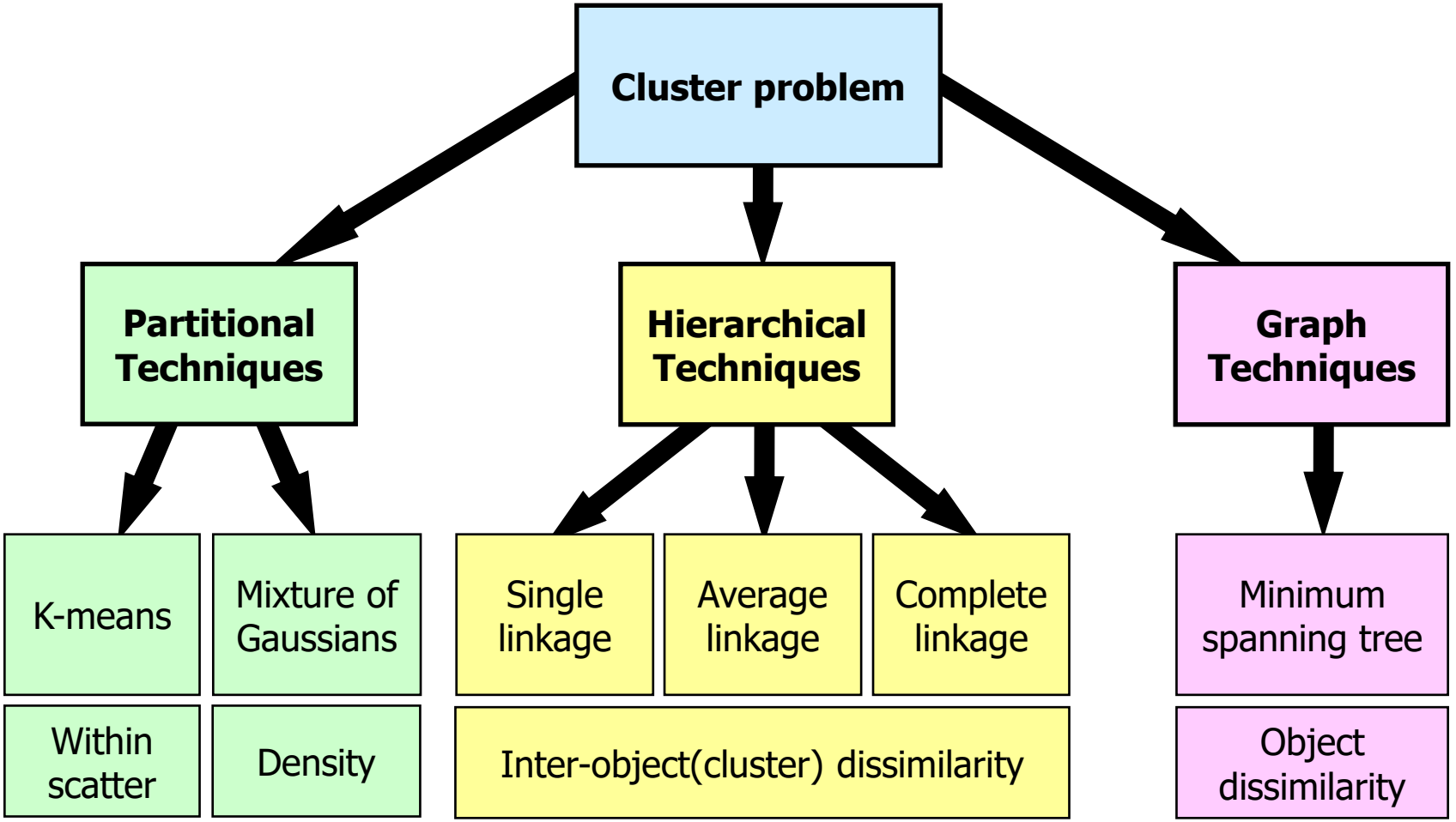
Clustering techniques



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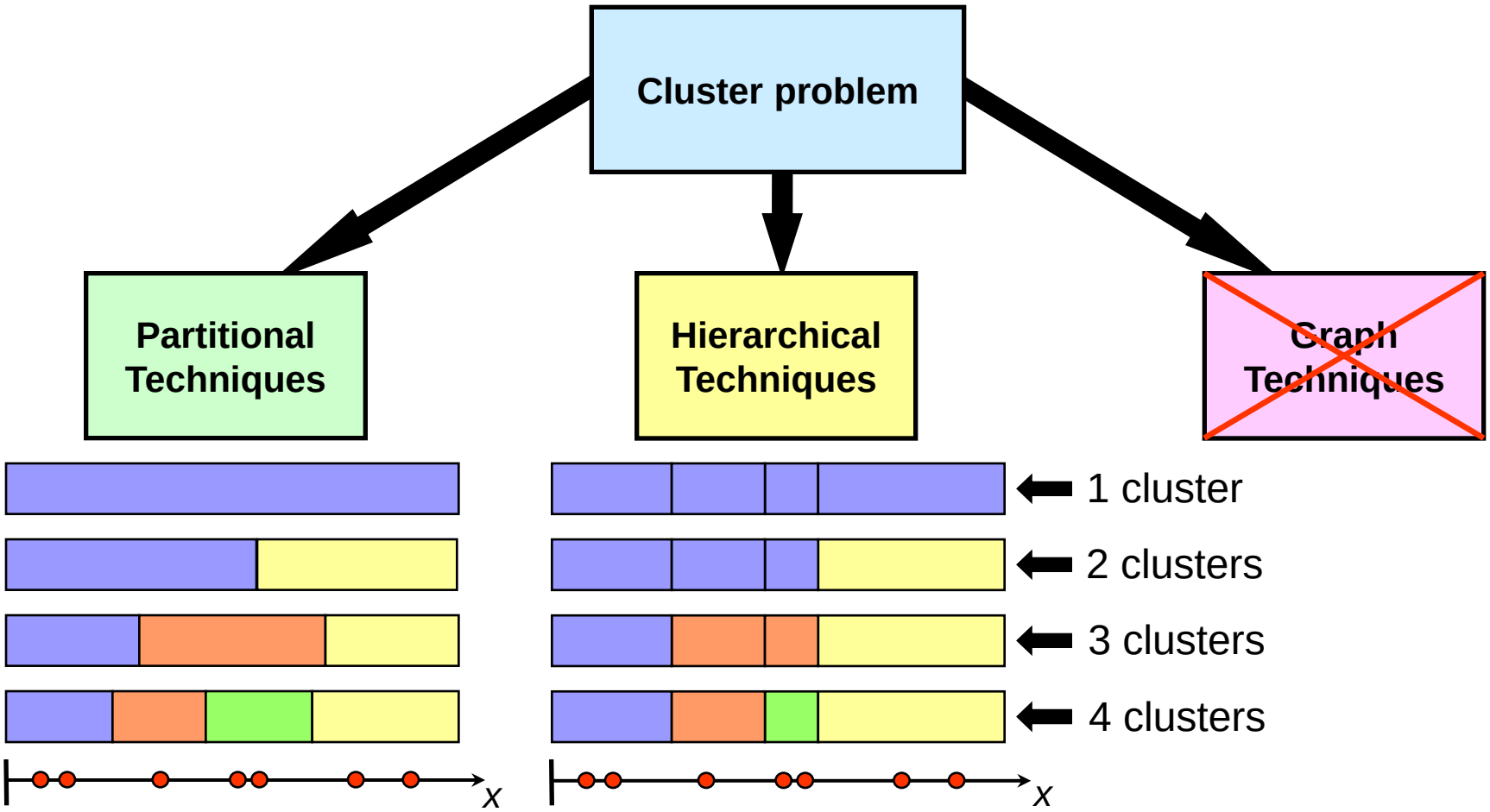
Clustering techniques (2)



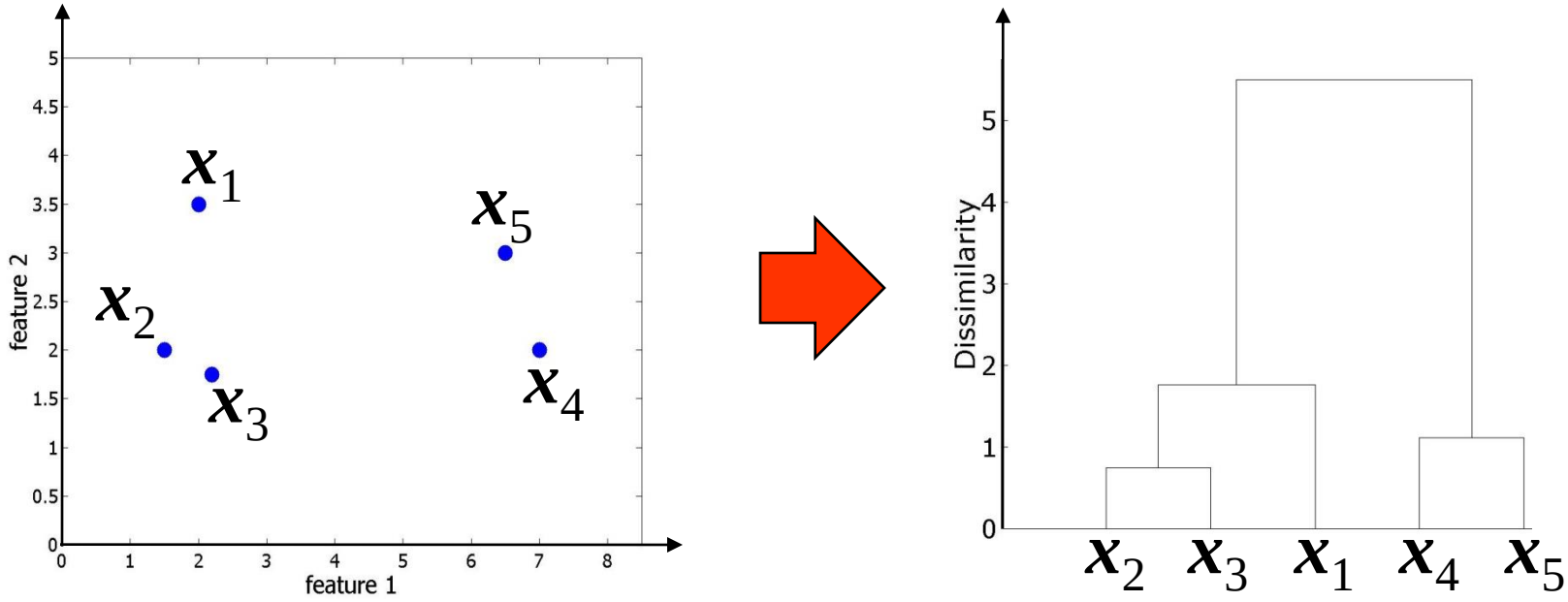
Hierarchical clustering

Input:

- dataset, ***X***: [*n* x *p*], or directly:
- dissimilarity matrix, ***D***: [*n* x *n*]
- linkage type

Output:

- dendrogram



Hierarchical clustering (2)

- **Algorithm** (agglomerative clustering)
  - Start: all objects of ***X*** in a separate cluster
  - Clustering: combine the 2 clusters with

    the shortest distance in dissimilarity matrix, ***D***
  - Distance between clusters is based on linkage type:
    - single, complete, average, …
  - Repeat until only 1 cluster is left

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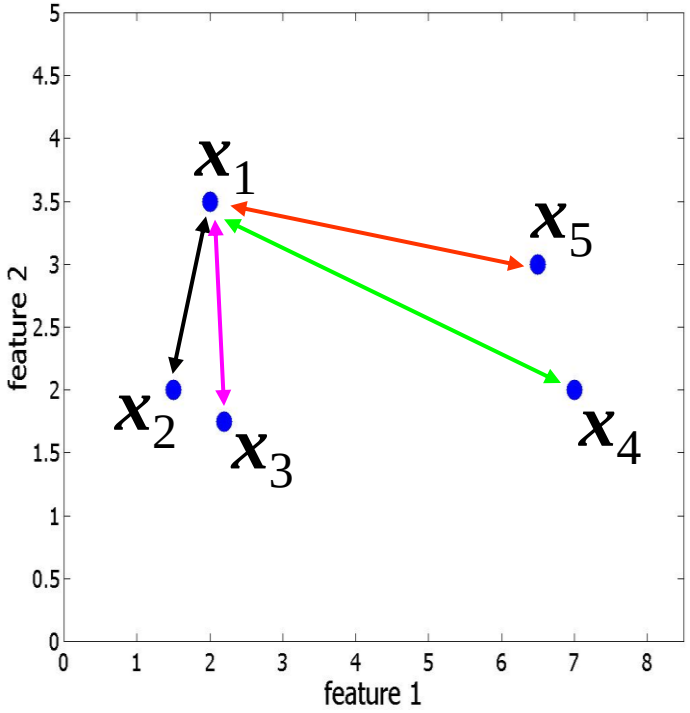
Hierarchical clustering (3)

Dataset

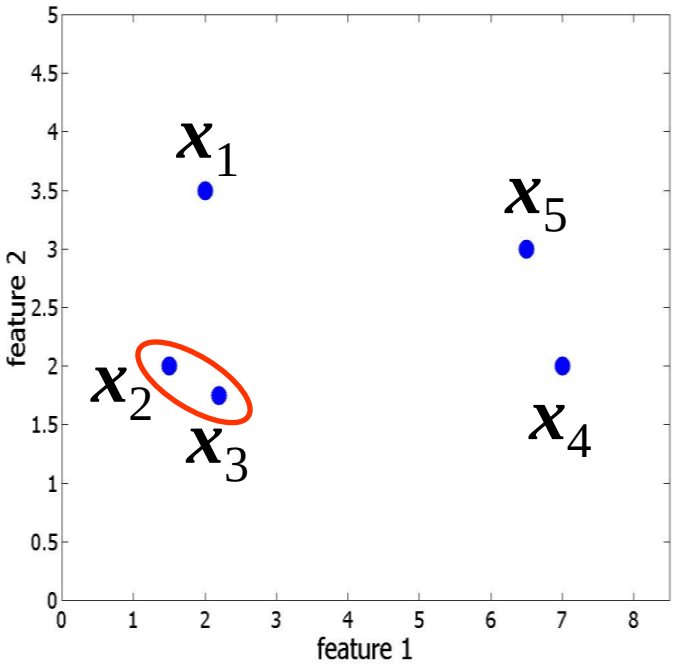


Euclidean distance matrix, ***D***

	x_1	x_2	x_3	x_4	x_5
x_1	0.00	1.58	1.76	5.22	4.53
x_2		0.00	0.74	5.50	5.10
x_3			0.00	4.81	4.48
x_4				0.00	1.12
x_5					0.00

Hierarchical clustering (4)

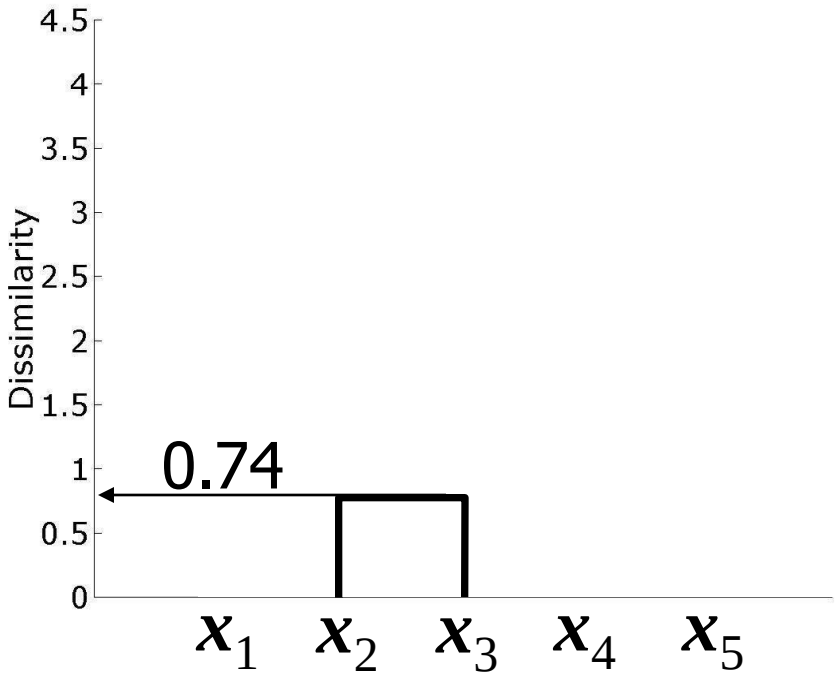
- **Step 1:**
  Find the most similar pair of objects: $\min_{(i,j)}\{d(i,j)\} = d(2,3)$



	x_1	x_2	x_3	x_4	x_5
x_1	0.00	1.58	1.76	5.22	4.53
x_2		0.00	0.74	5.50	5.10
x_3			0.00	4.81	4.48
x_4				0.00	1.12
x_5					0.00

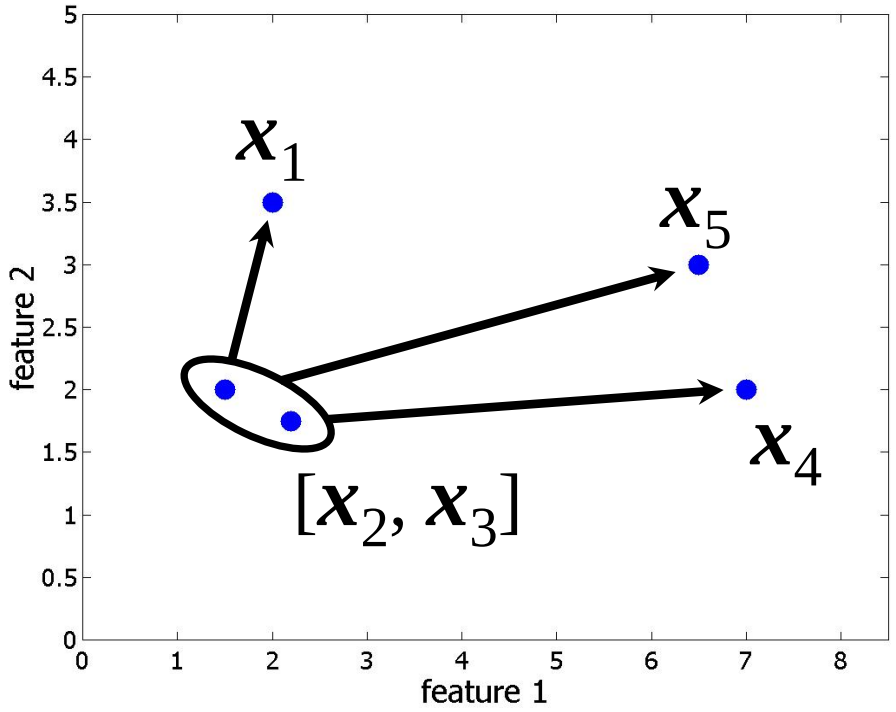
Hierarchical clustering (5)

- **Step 2:**
  Merge x_2 and x_3 into a single object, $[x_2, x_3]$;



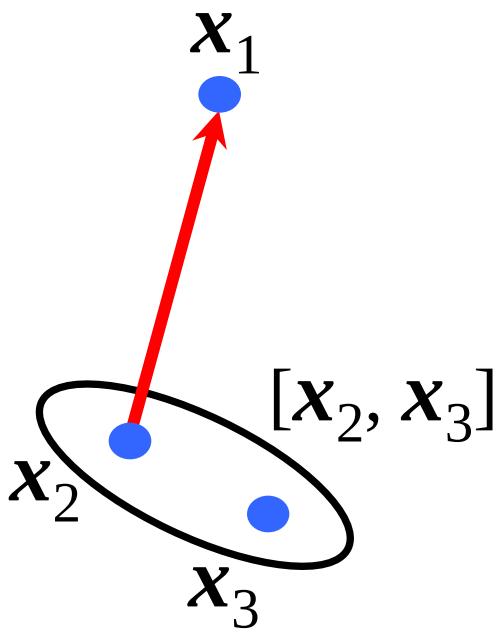
Hierarchical clustering (6)

- **Step 3:**
  Recompute $\boldsymbol{D}$ –
  what is the distance between $[x_2, x_3]$ and the rest?



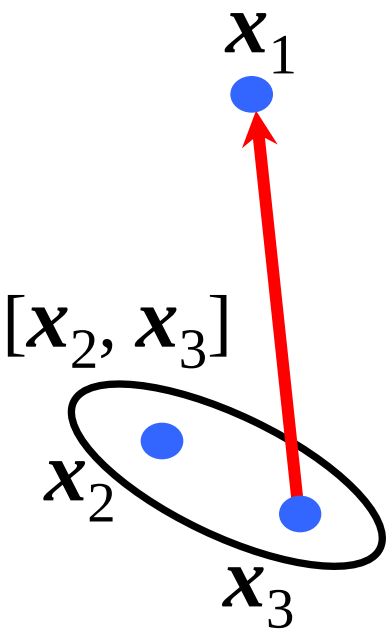
Hierarchical clustering (7)

- **Step 3:**
  Recompute $\boldsymbol{D}$ –
  single linkage: $d([\boldsymbol{x}_2,\boldsymbol{x}_3],\boldsymbol{x}_1) = \min(d(\boldsymbol{x}_1,\boldsymbol{x}_2),d(\boldsymbol{x}_1,\boldsymbol{x}_3))$



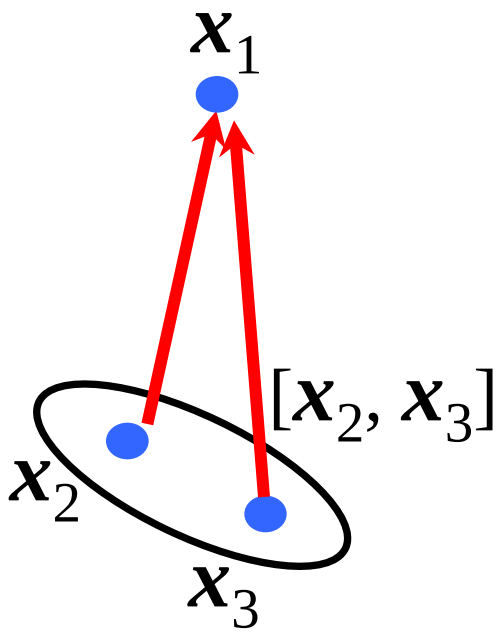
Hierarchical clustering (8)

- **Step 3:**
  Recompute $\boldsymbol{D}$ –
  complete linkage: $d([\boldsymbol{x}_2,\boldsymbol{x}_3],\boldsymbol{x}_1) = \max(d(\boldsymbol{x}_1,\boldsymbol{x}_2),d(\boldsymbol{x}_1,\boldsymbol{x}_3))$



Hierarchical clustering (9)

- **Step 3:**
  Recompute $\boldsymbol{D}$ –
  average linkage: $d([x_2,x_3],x_1) = \text{mean}(d(x_1,x_2),d(x_1,x_3))$



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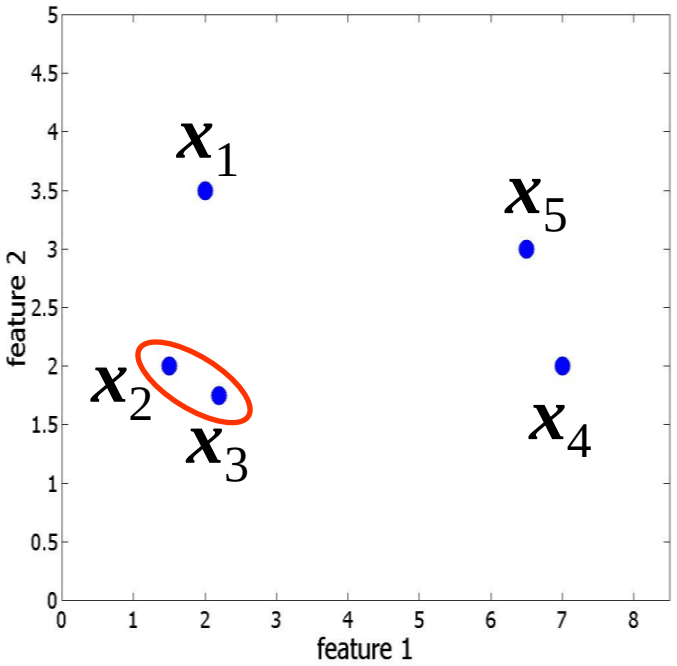
Hierarchical clustering (10a)

- **Step 3:**
  Recompute D – **single linkage:**



	x_1	x_2	x_3	x_4	x_5
x_1	0.00	1.58	1.76	5.22	4.53
x_2		0.00	0.74	5.50	5.10
x_3			0.00	4.81	4.48
x_4				0.00	1.12
x_5					0.00

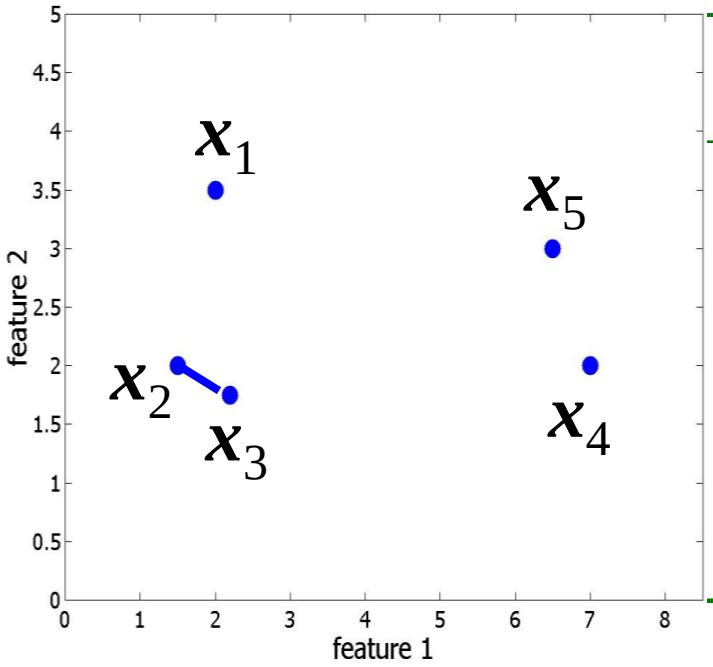
Hierarchical clustering (10b)

- **Step 3:**
  Recompute D – **single linkage:**

	x_1	$[x_2,x_3]$	x_4	x_5
x_1	0.00	1.58	5.22	4.53
$[x_2,x_3]$		0.00	4.81	4.48
x_4			0.00	1.12
x_5				0.00

Hierarchical clustering (11)

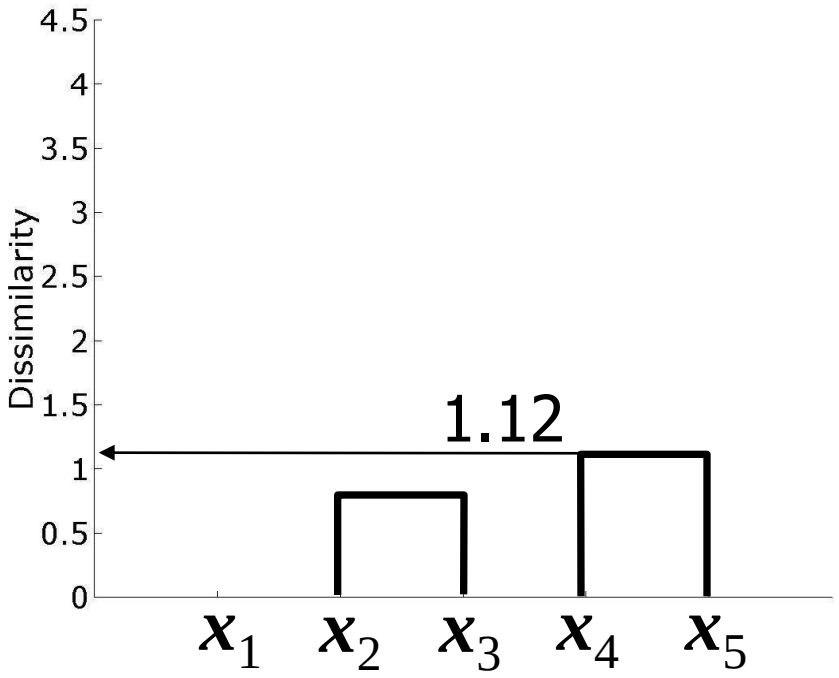
- **Repeat, step 1:**
  Find the most similar pair of objects: $\min_{(i,j)}\{d(i,j)\} = d(4,5)$



	x_1	$[x_2,x_3]$	x_4	x_5
x_1	0.00	1.58	5.22	4.53
$[x_2,x_3]$	1.58	0.00	4.81	4.48
x_4	5.22	4.81	0.00	1.12
x_5	4.53	4.48	1.12	0.00

Hierarchical clustering (12)

- **Repeat, step 2:**
  Merge x_4 and x_5 into a single object, $[x_4,x_5]$;



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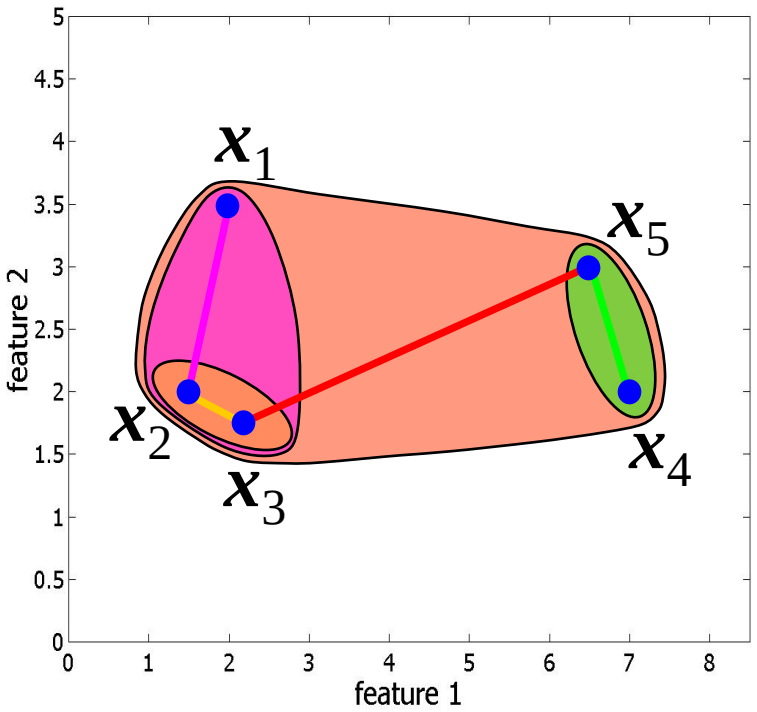
Hierarchical clustering (13)

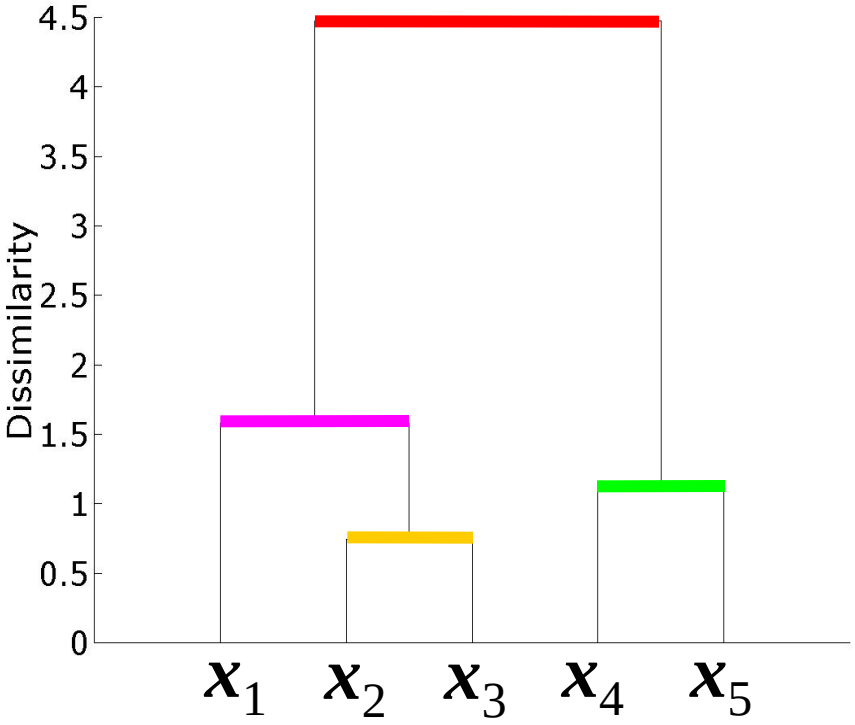
- **Repeat, step 3:**
  Recompute $\boldsymbol{D}$ (single linkage):

	x_1	$[x_2,x_3]$	$[x_4,x_5]$
x_1	0.00	1.58	4.53
$[x_2,x_3]$		0.00	4.48
$[x_4,x_5]$			0.00

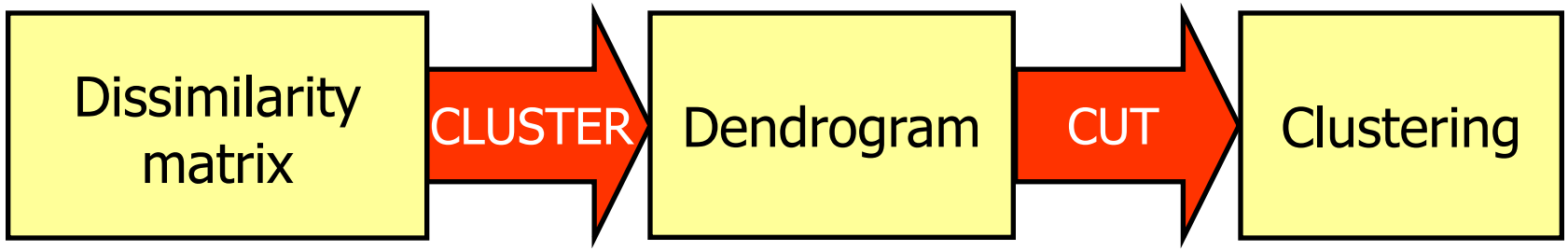
Hierarchical clustering (14)

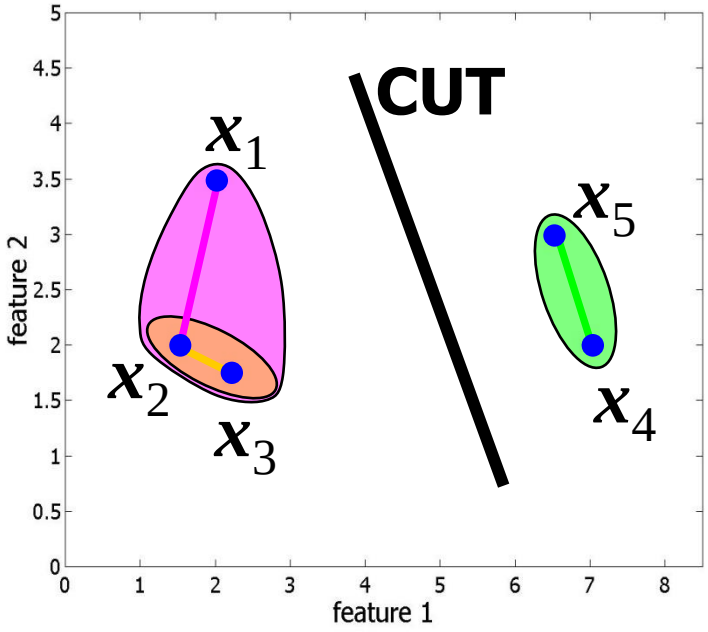
- Repeat steps 1-3 until a single cluster remains

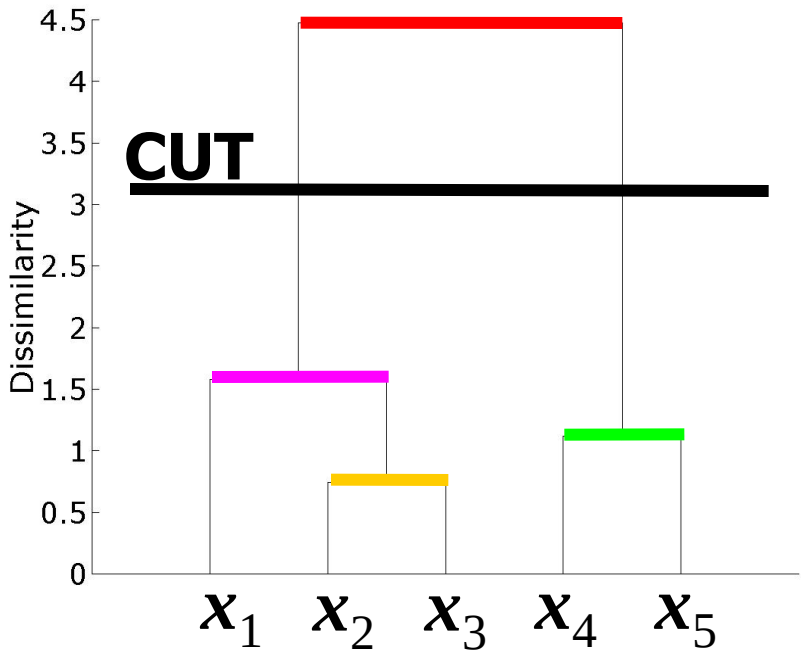




Hierarchical clustering (15)



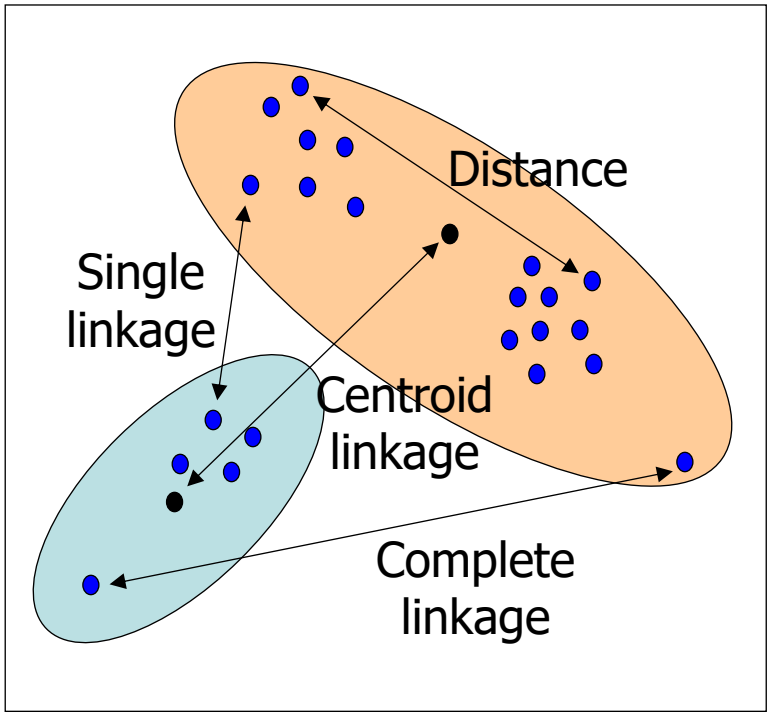




Hierarchical clustering (16)

- Hierarchical clustering: repeatedly group closest clusters

- Important choices:
  - *Distance measure*
    between objects:
    Euclidean, correlation,
    Hamming, Minkowski, ...
  - *Linkage*
    between clusters:
    single, average (centroid), complete



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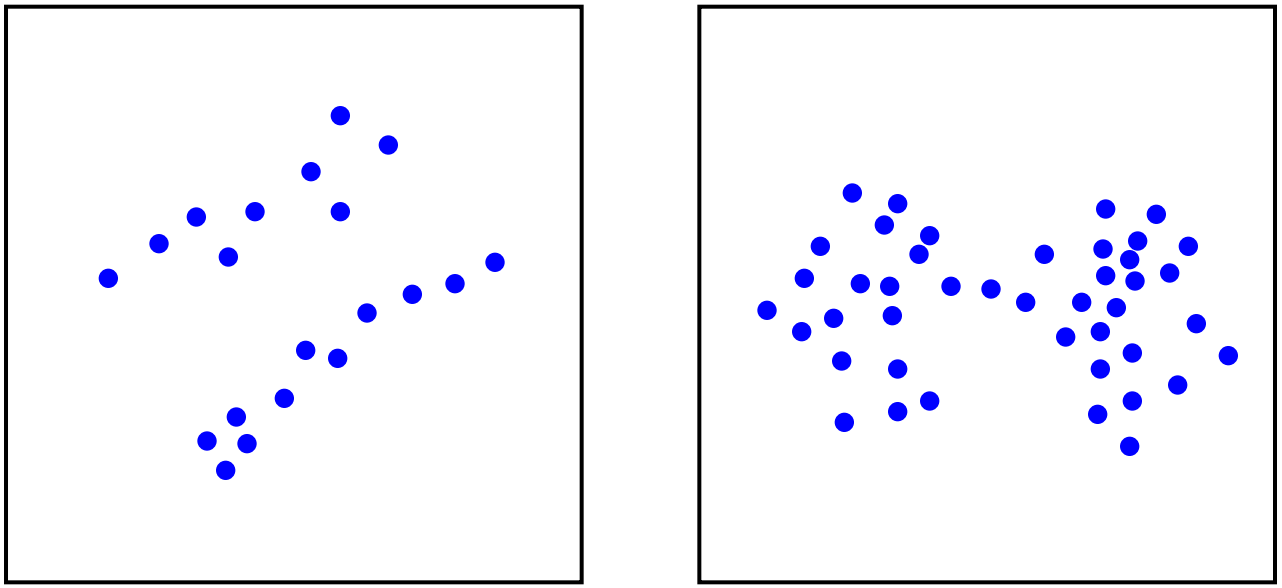
Linkage and cluster shape



Complete linkage

Single linkage

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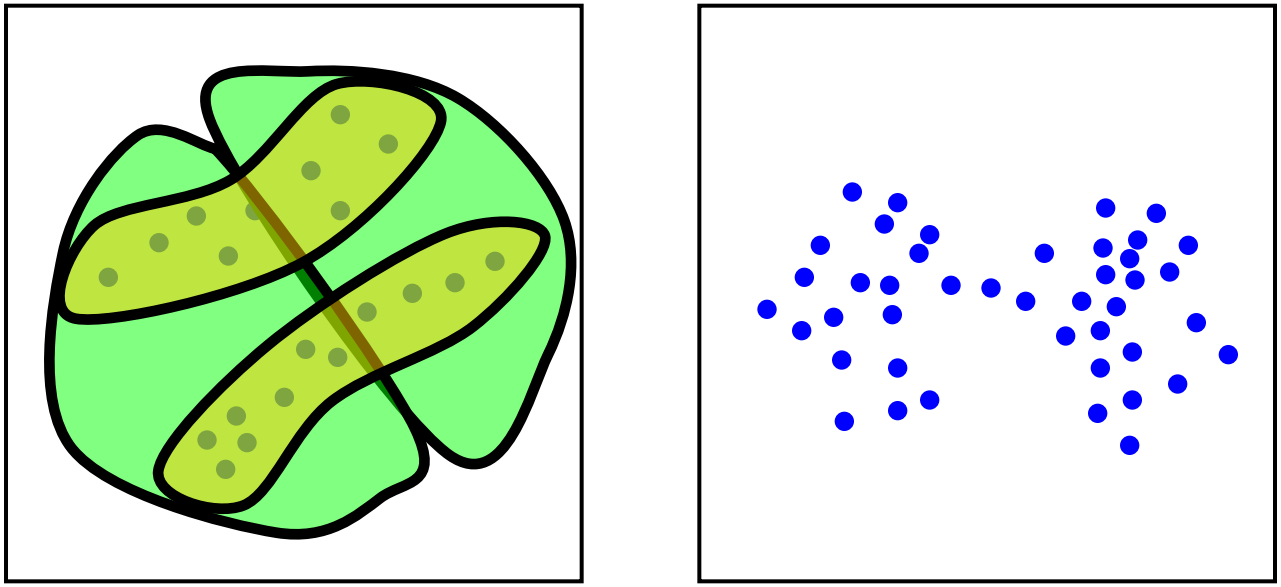
Linkage and cluster shape (2)



Complete linkage

Single linkage

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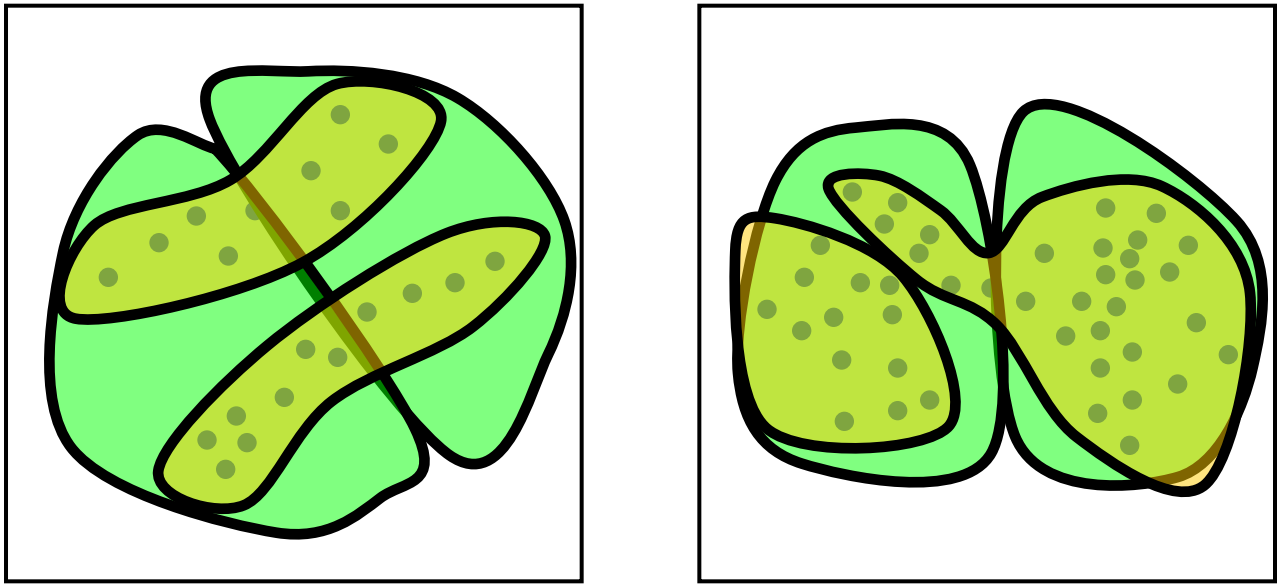
Linkage and cluster shape (3)



Complete linkage

Single linkage

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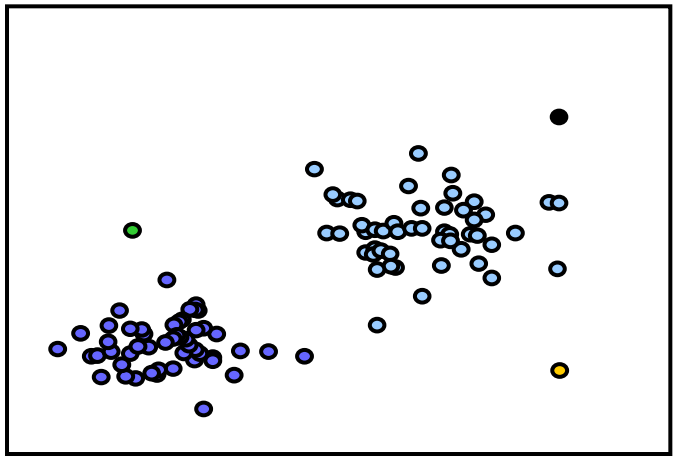
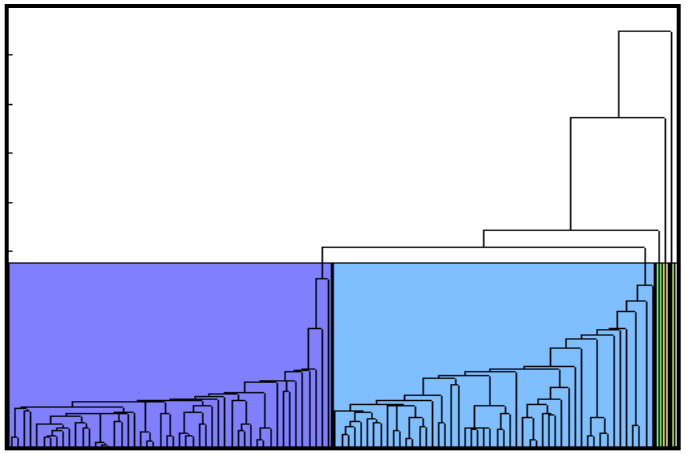
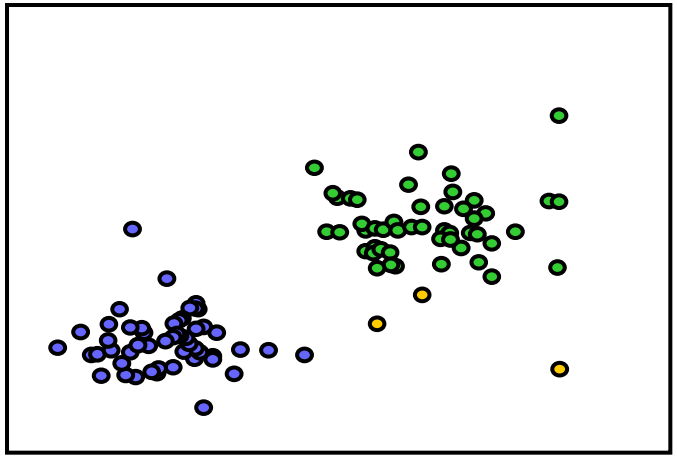
Linkage and outliers

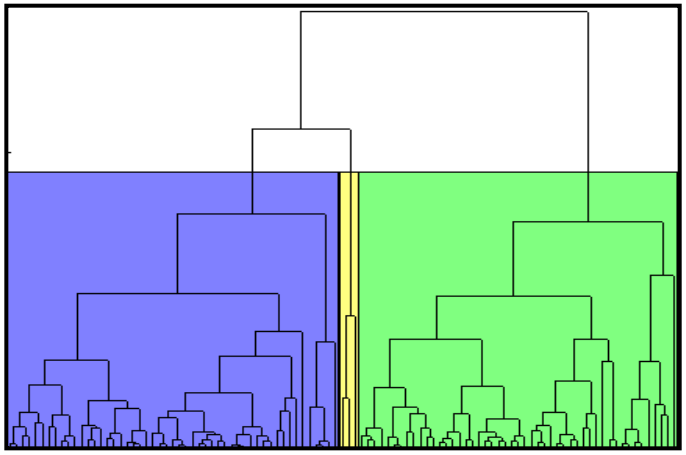
Single linkage





Complete linkage





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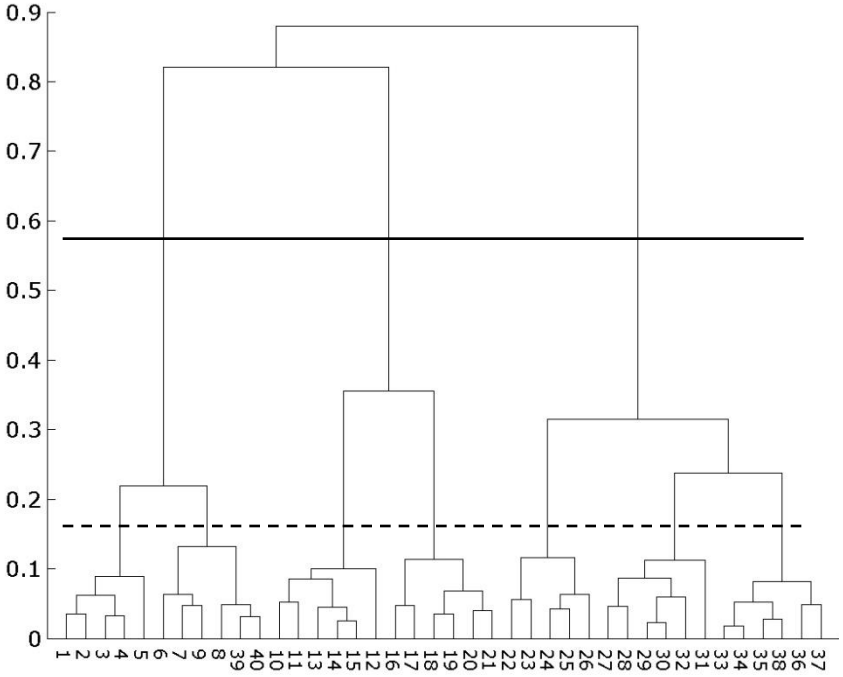
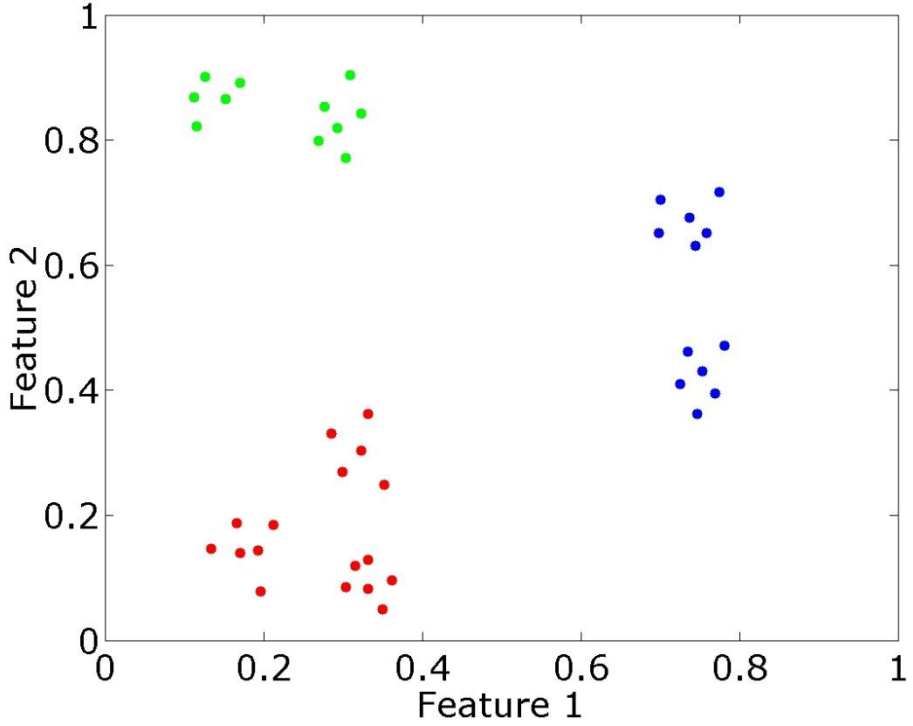
Hierarchical clustering examples

Euclidean, complete linkage





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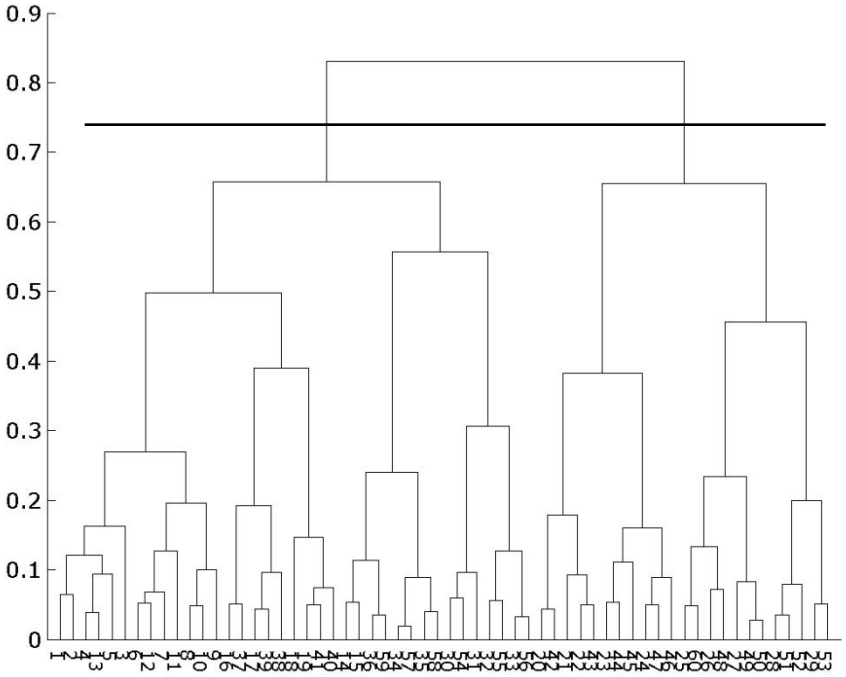
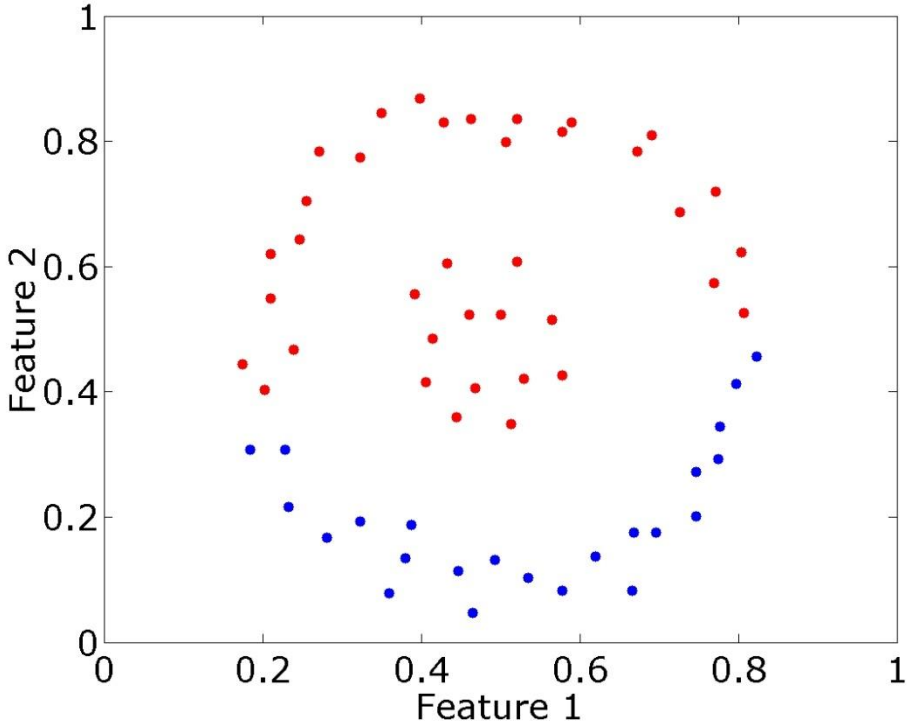
Hierarchical clustering examples (2)

Euclidean, complete linkage





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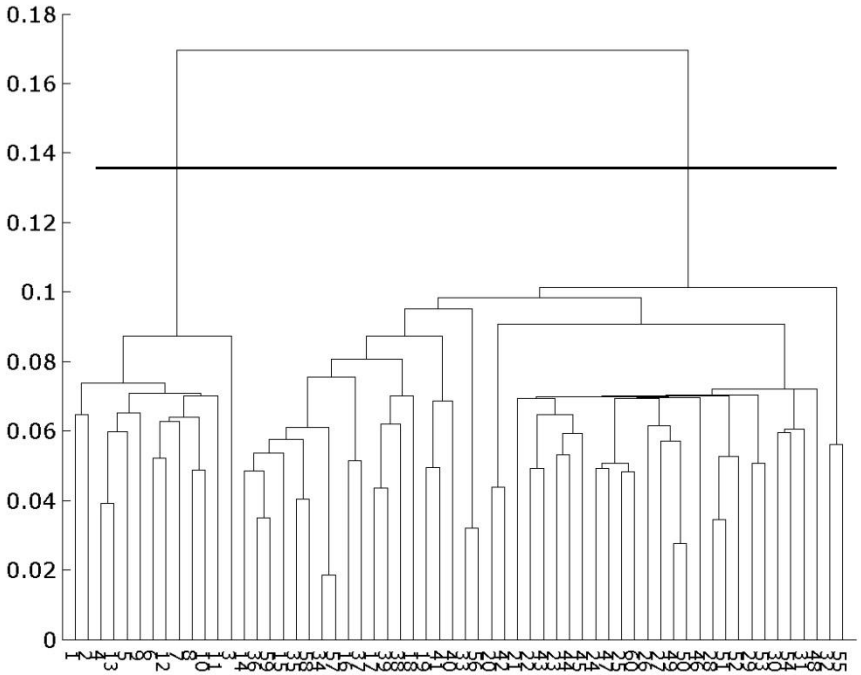
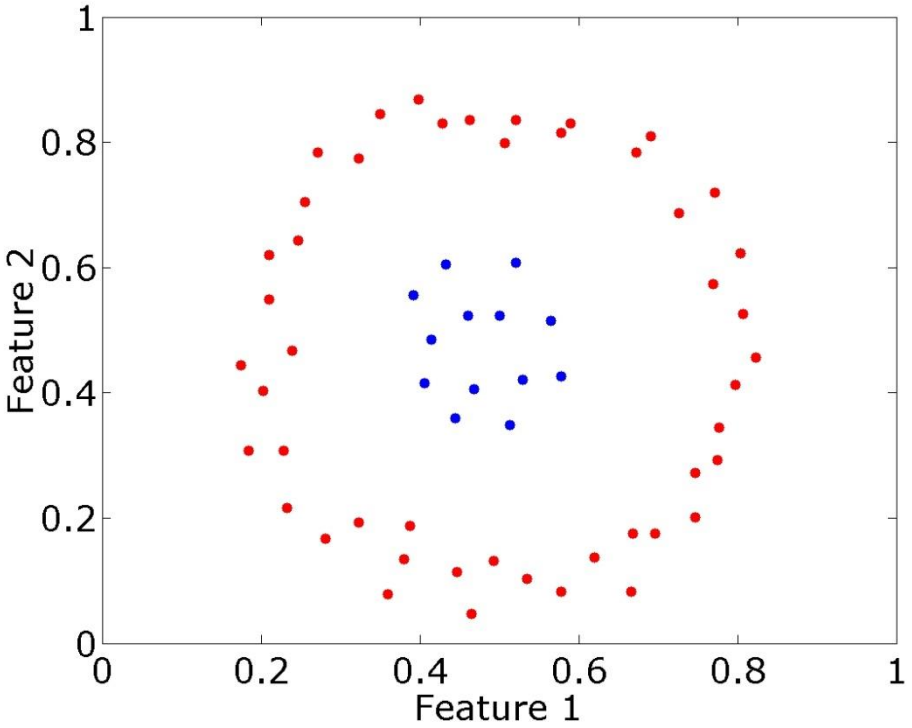
Hierarchical clustering examples (3)

Euclidean, single linkage





Hierarchical clustering (17)

- Advantages:
  - dendrogram gives overview of all possible clusterings
  - linkage type allows to find clusters of varying shapes (convex and non-convex)
  - different dissimilarity measures can be used

- Disadvantages:
  - computationally intensive:
    $O(n^2)$ in complexity and memory
  - clusterings limited to “hierarchical nestings”

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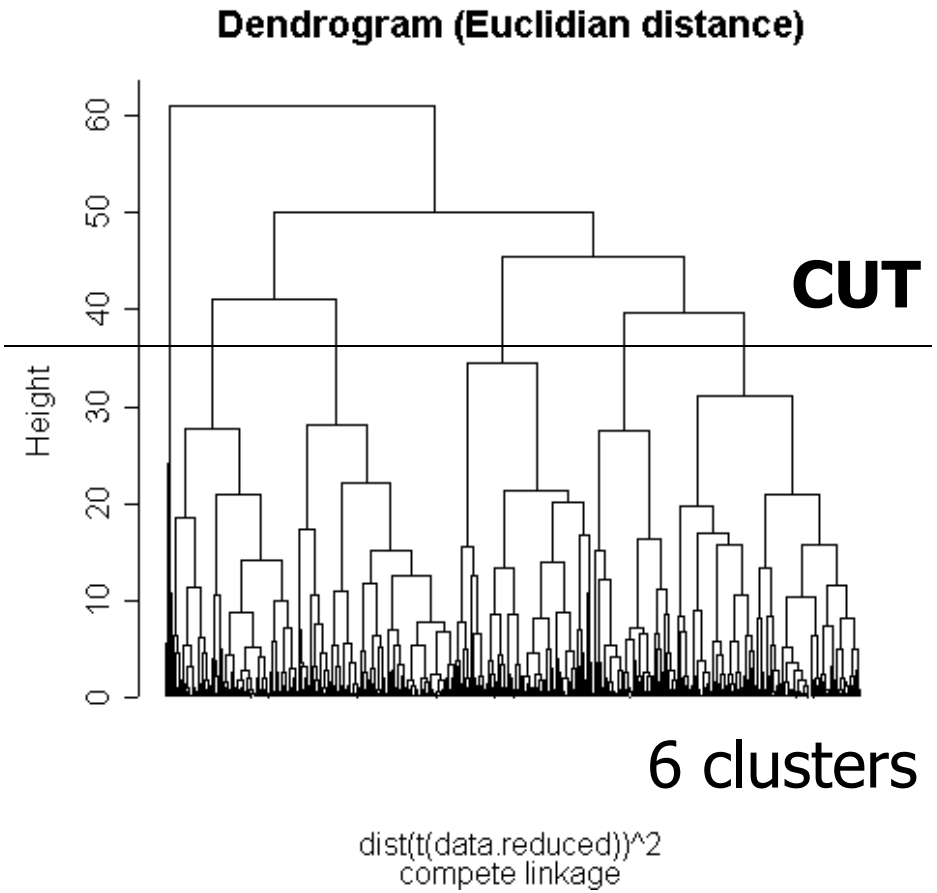
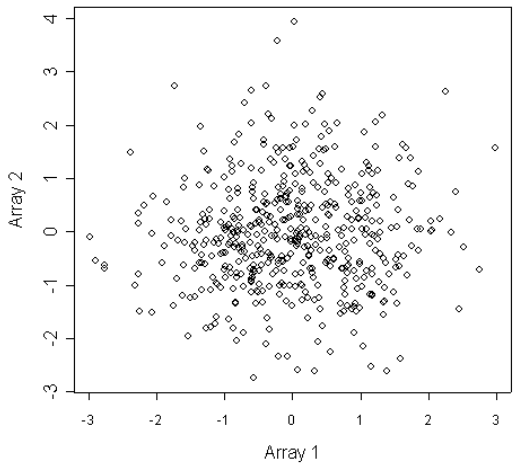
Hierarchical clustering: warning

- Cluster 500 genes, 5 arrays:



Data were random …



Validation is needed

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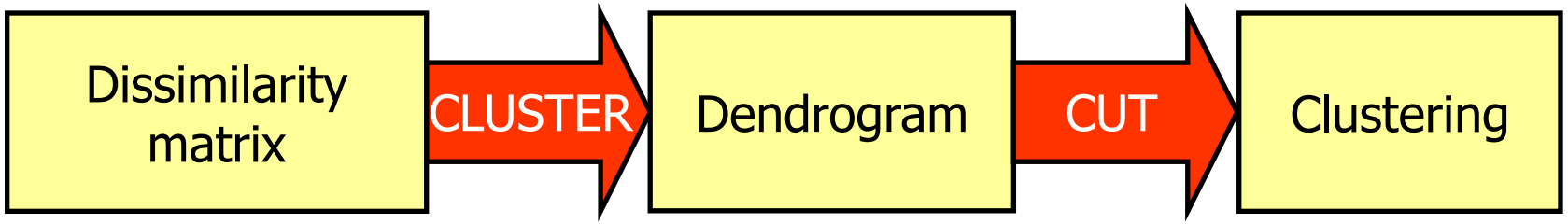
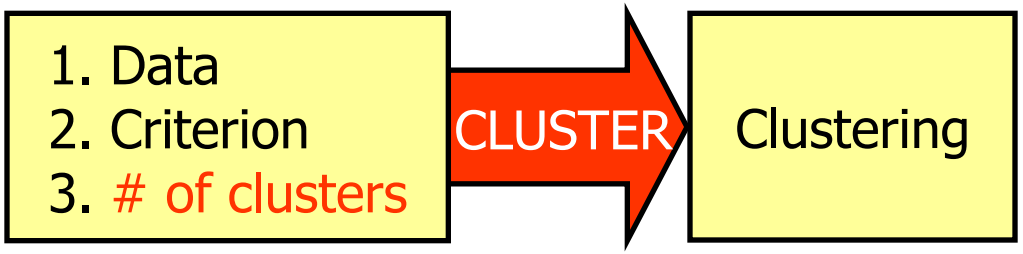
Exercise 2.14-2.19

Sum-of-squares clustering

- Hierarchical:



- Sum-of-squares:



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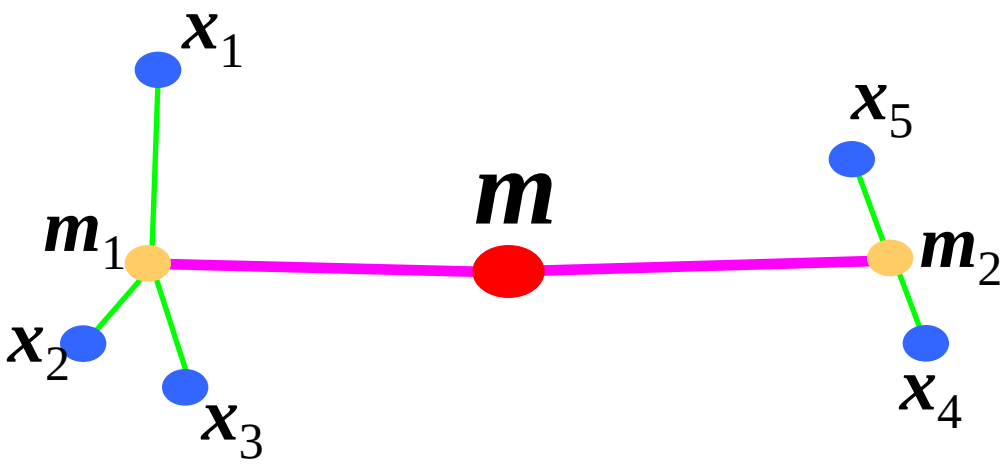
Sum-of-squares clustering (2)

- Within and between scatter:

$$\boldsymbol{S}_w = \sum_{i=1}^{C} \frac{n_i}{n} \Sigma_i \quad (n_1 = 3, n_2 = 2, n = 5, C = 2)$$

$$\boldsymbol{S}_B = \sum_{i=1}^{C} \frac{n_i}{n} (\boldsymbol{m}_i - \boldsymbol{m})(\boldsymbol{m}_i - \boldsymbol{m})^T, \ \boldsymbol{m} = \sum_{i=1}^{C} \frac{n_i}{n} \boldsymbol{m}_i$$



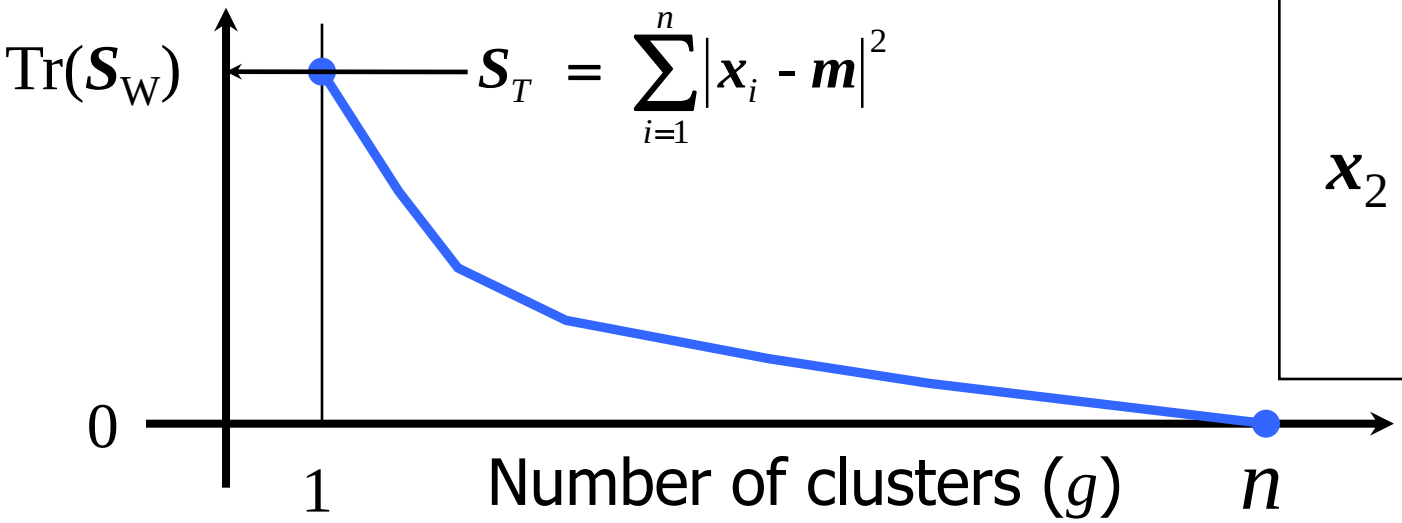
BioSB

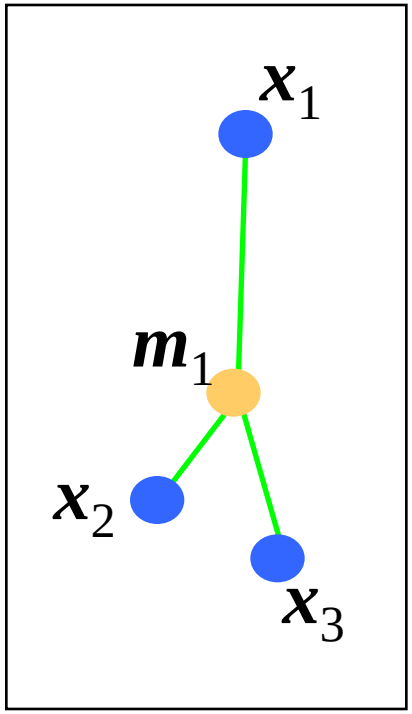
K-means

- Minimize: $\mathrm{Tr}(\mathbf{S}_W) = \frac{1}{n}\sum_{j=1}^{g}\mathbf{S}_j$

$$\boldsymbol{S}_j = \sum_{i=1}^{n_j}\left|\boldsymbol{x}_i - \boldsymbol{m}_j\right|^2$$

(sum of per cluster variances)





K-means (2)

- Iterative procedure to search for $\min(\mathrm{Tr}(\boldsymbol{S}_\mathrm{W}))$:
  1. choose number of clusters (g)
  2. position prototypes (m_j, $j=1,\ldots,g$) randomly
  3. assign samples to closest prototype
  4. compute mean of samples assigned to same prototype: new prototype position

  Repeat steps 3 and 4 as long as prototypes move

BioSB

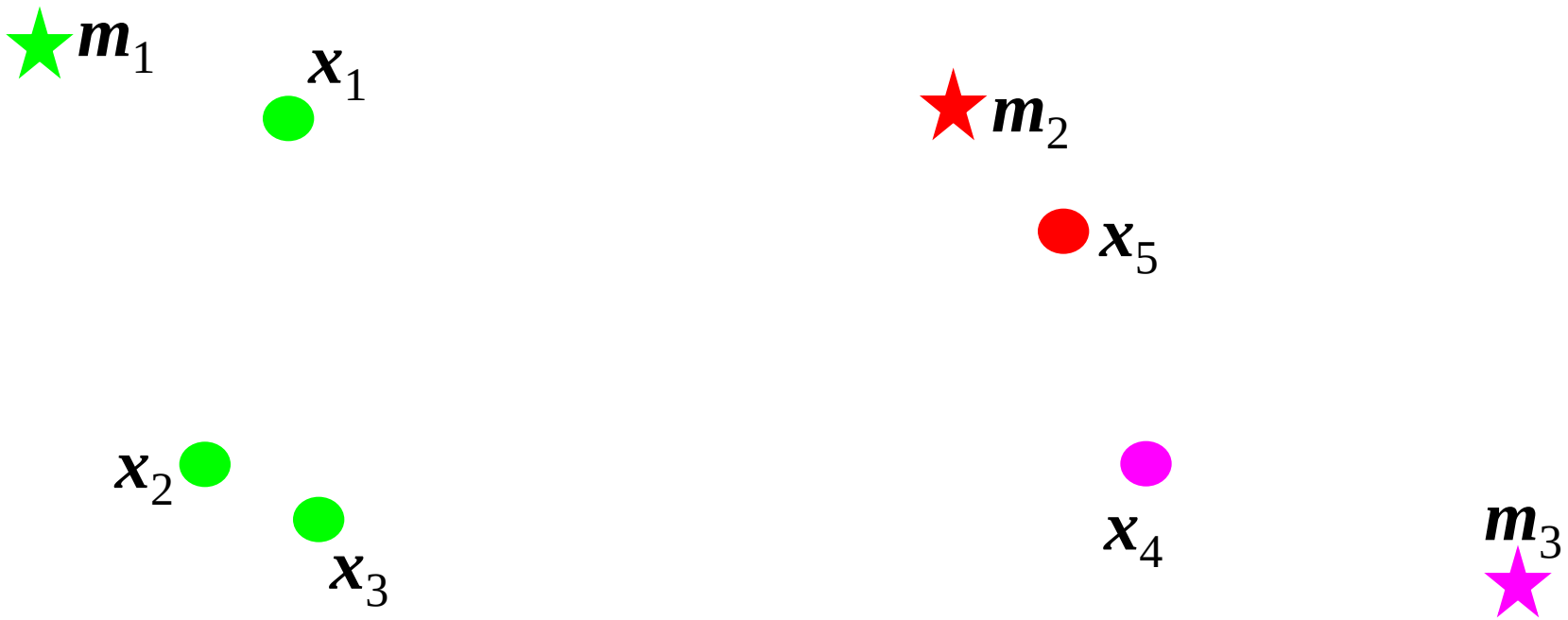
K-means (3)

- **Step 1:** Choose number of clusters/prototypes
- **Step 2:** Position prototypes randomly

BioSB

K-means (4)

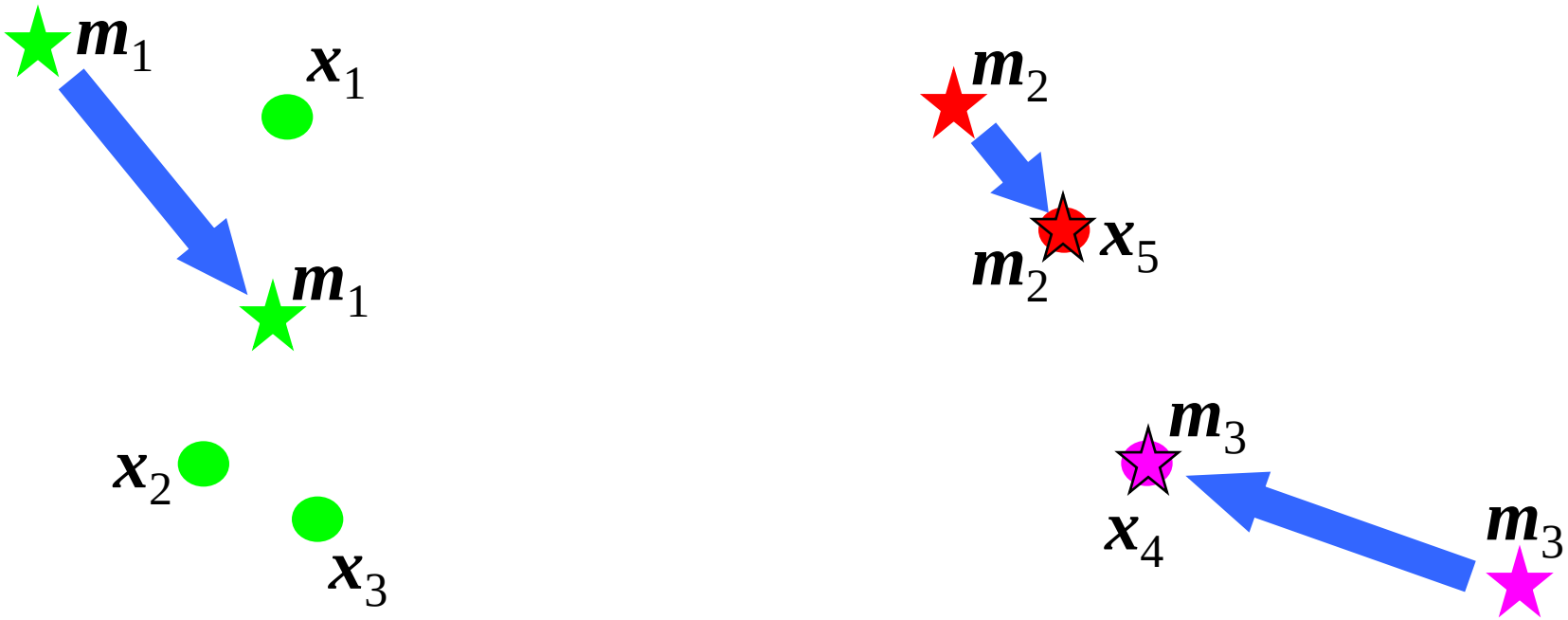
- **Step 3:** Assign samples to closest prototype



BioSB

K-means (5)

- **Step 4:** Compute mean of samples assigned to same prototype: new prototype positions



BioSB

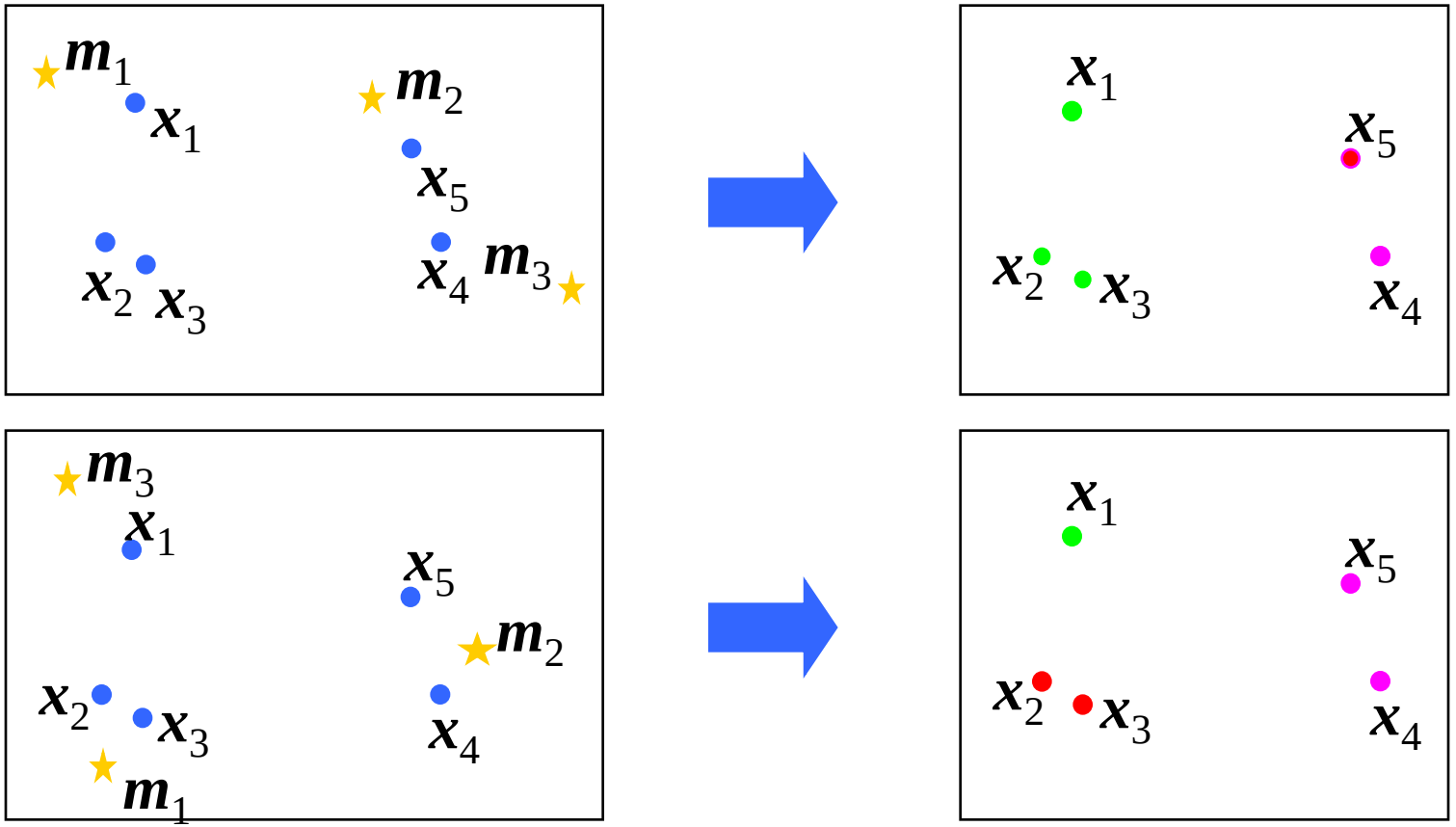
K-means (6)

- **Repeat** as long as prototype positions change**:**
  - **Step 3:** Assign samples
  - **Step 4:** Recompute prototype positions

BioSB

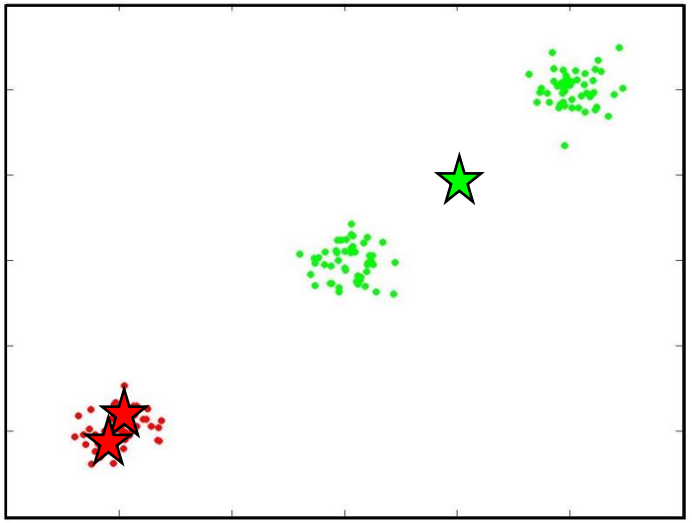
K-means problems

- Clustering depends on initialization



K-means problems (2)

- Algorithm can get stuck in local minima

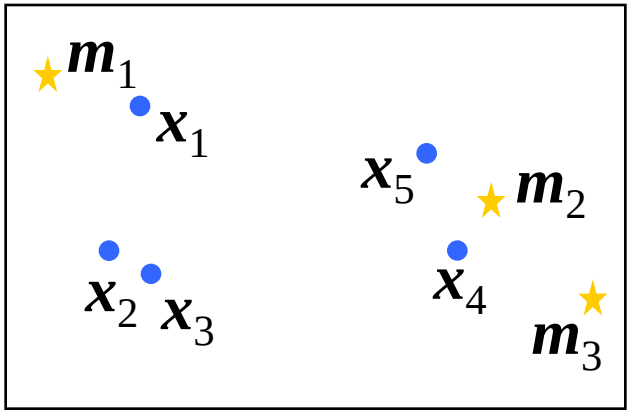


- Solution:
  - start from I different random initialisations
  - keep the best clustering (lowest $\mathrm{Tr}(\boldsymbol{S}_\mathrm{W})$)
  - For high-dimensional data, many restarts can be necessary (e.g. I = 100)

BioSB

K-means problems (3)

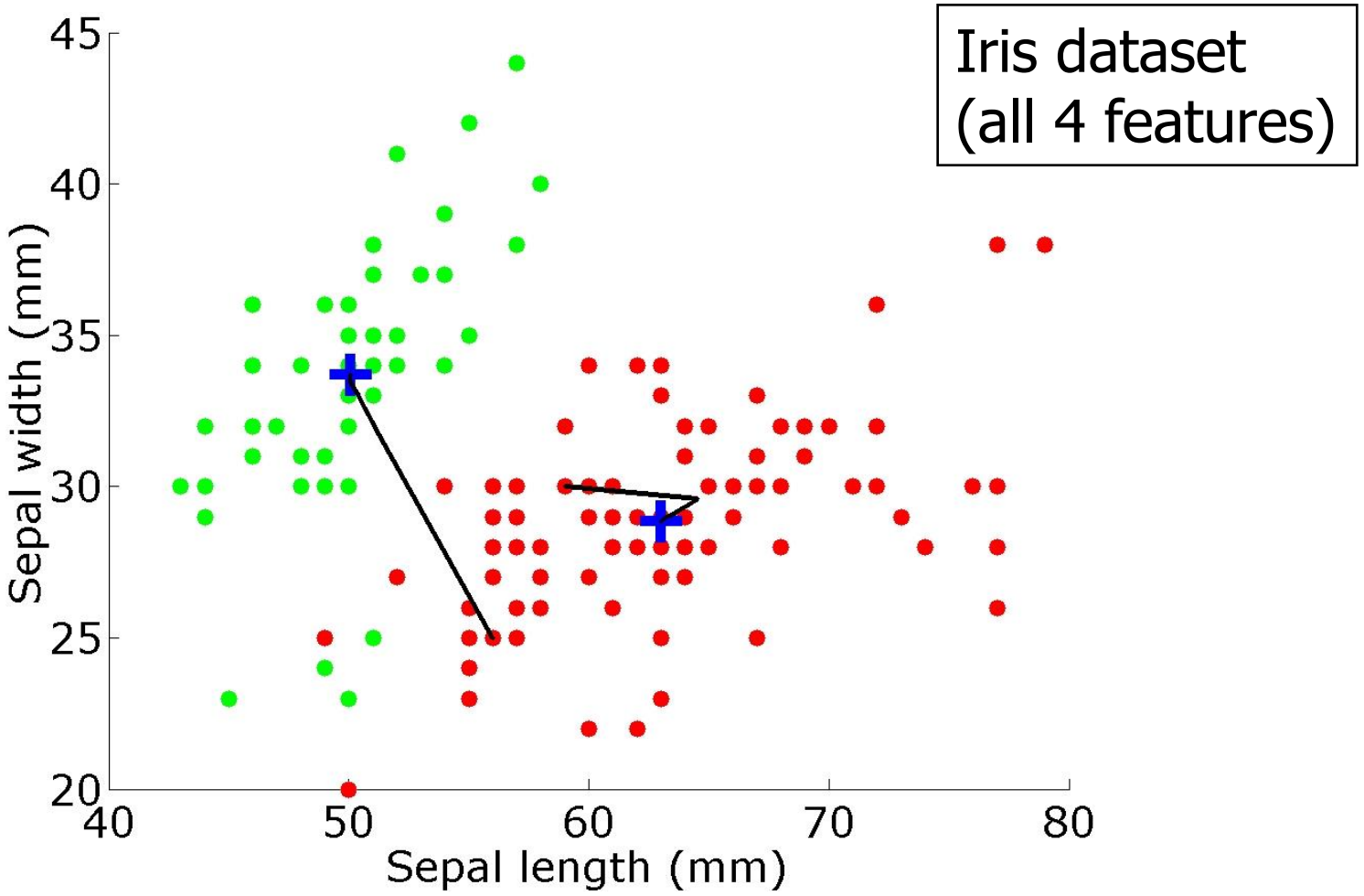
- Clusters can loose all samples



- Possible solution:
  - remove cluster and continue with $g - 1$ means
  - alternatively, split largest cluster into two
    or add a random cluster to continue with g means

BioSB

K-means example



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Advantages/disadvantages: *K*-means

- Disadvantages:
  - Finds only convex clusters (“round shapes”)
  - Sensitive to initialization
  - Can get stuck in local minima

- Advantages:
  - Very simple
  - Fast

BioSB

Recapitulation

- Clustering is way to detect *natural* groups in data
- What is natural is partly subjective
- We looked at:
  - *Hierarchical clustering*
  - *Sum of squares* (k-means) clustering
- Hierarchical clustering:
  - *dendrogram* shows a complete hierarchy of possible clusterings
  - computionally intensive
- *K*-means
  - fast
  - sensitive to *initialization* and *local minima*

BioSB

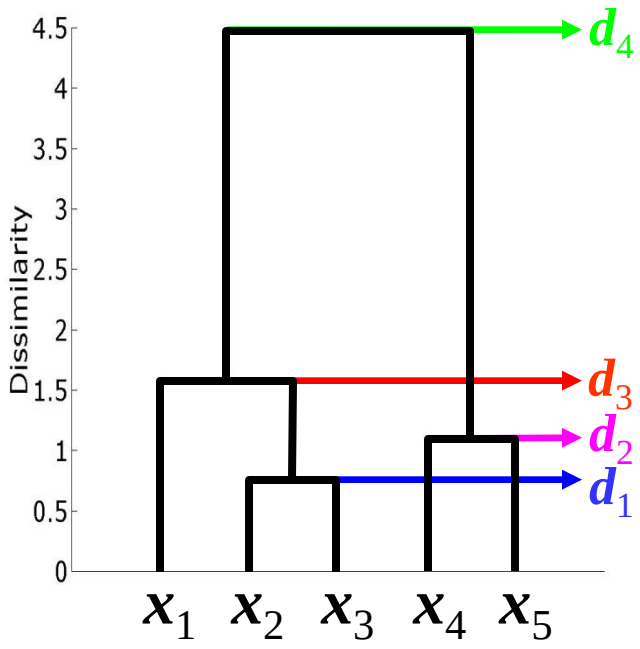
Cluster validation

- Cluster validation:
  - Checking whether grouping is really present
  - Choosing the optimal number of clusters
- A difficult problem – the ground truth is not known (since we do not know the object labels)!
- Methods:
  - Distortion measures:
    - Does clustering approximate structure in data?
  - Validity measures:
    - Davies-Bouldin index
  - Fusion graph
  - Gap statistic

BioSB

Distortion measures

- How well does a dendrogram capture structure in data?



d^*	x_1	x_2	x_3	x_4	x_5
x_1	0	d_3	d_3	d_4	d_4
x_2		0	d_1	d_4	d_4
x_3			0	d_4	d_4
x_4				0	d_2
x_5					0

Distortion measures (2)

- Measure of distortion: Pearson correlation of $\boldsymbol{d}$ and $\boldsymbol{d}^*$

$$\rho(\boldsymbol{d},\boldsymbol{d}^*) = \frac{\mathrm{cov}(\boldsymbol{d},\boldsymbol{d}^*)}{\sqrt{\mathrm{var}(\boldsymbol{d})\mathrm{var}(\boldsymbol{d}^*)}} \in [-1,1]$$

$\boldsymbol{d}$

	x_1	x_2	x_3	x_4	x_5
x_1	0.00	1.58	1.76	5.22	4.53
x_2		0.00	0.74	5.50	5.10
x_3			0.00	4.81	4.48
x_4				0.00	1.12
x_5					0.00

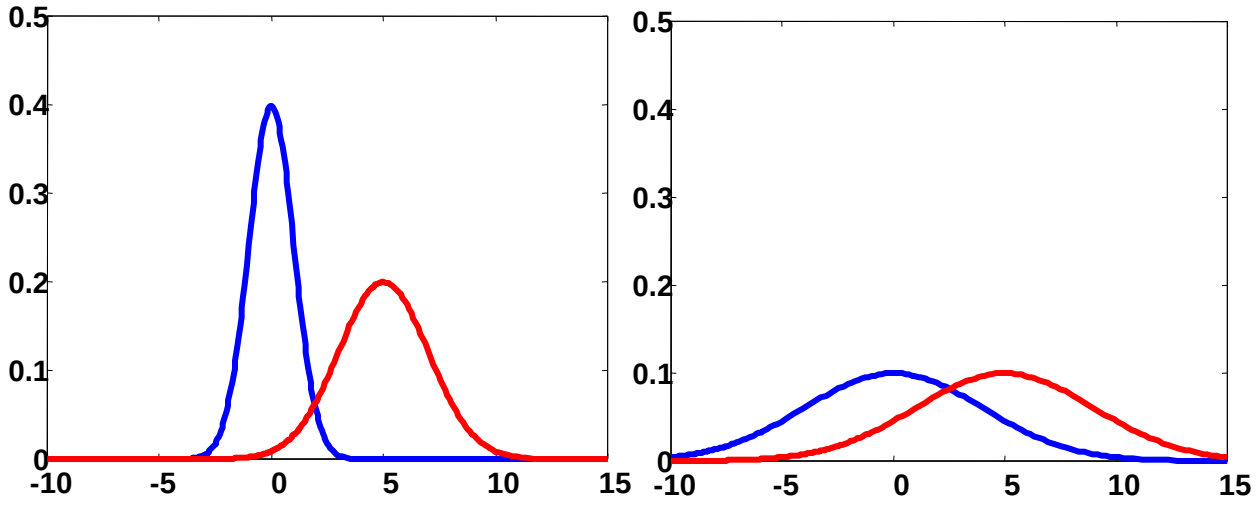
$\boldsymbol{d}^*$

	x_1	x_2	x_3	x_4	x_5
x_1	0	d_3	d_3	d_4	d_4
x_2		0	d_1	d_4	d_4
x_3			0	d_4	d_4
x_4				0	d_2
x_5					0

BioSB

Validity measures

- Many are based on within and between group scatter
- The larger the between group scatter and the smaller the within group scatter, the better
- Example: Davies-Bouldin



Davies-Bouldin index

- Assumption: clusters are spherical
- For a good clustering, it should hold that:
  - objects are compactly organized within a cluster
  - clusters are far apart

- D.L. Davies and D.W. Bouldin, IEEE Transactions on Pattern Analysis and Machine Intelligence 1, pp. 224-227, 1979

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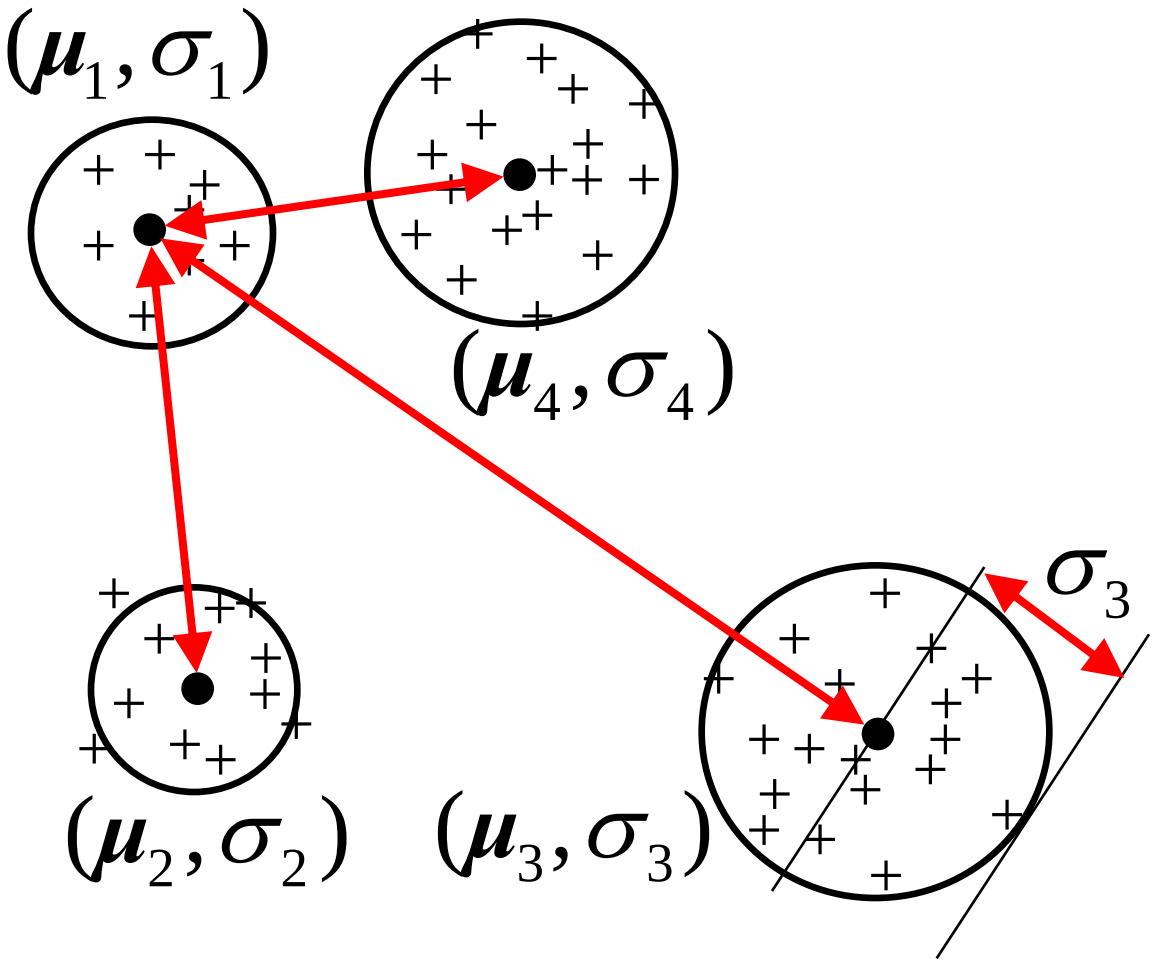
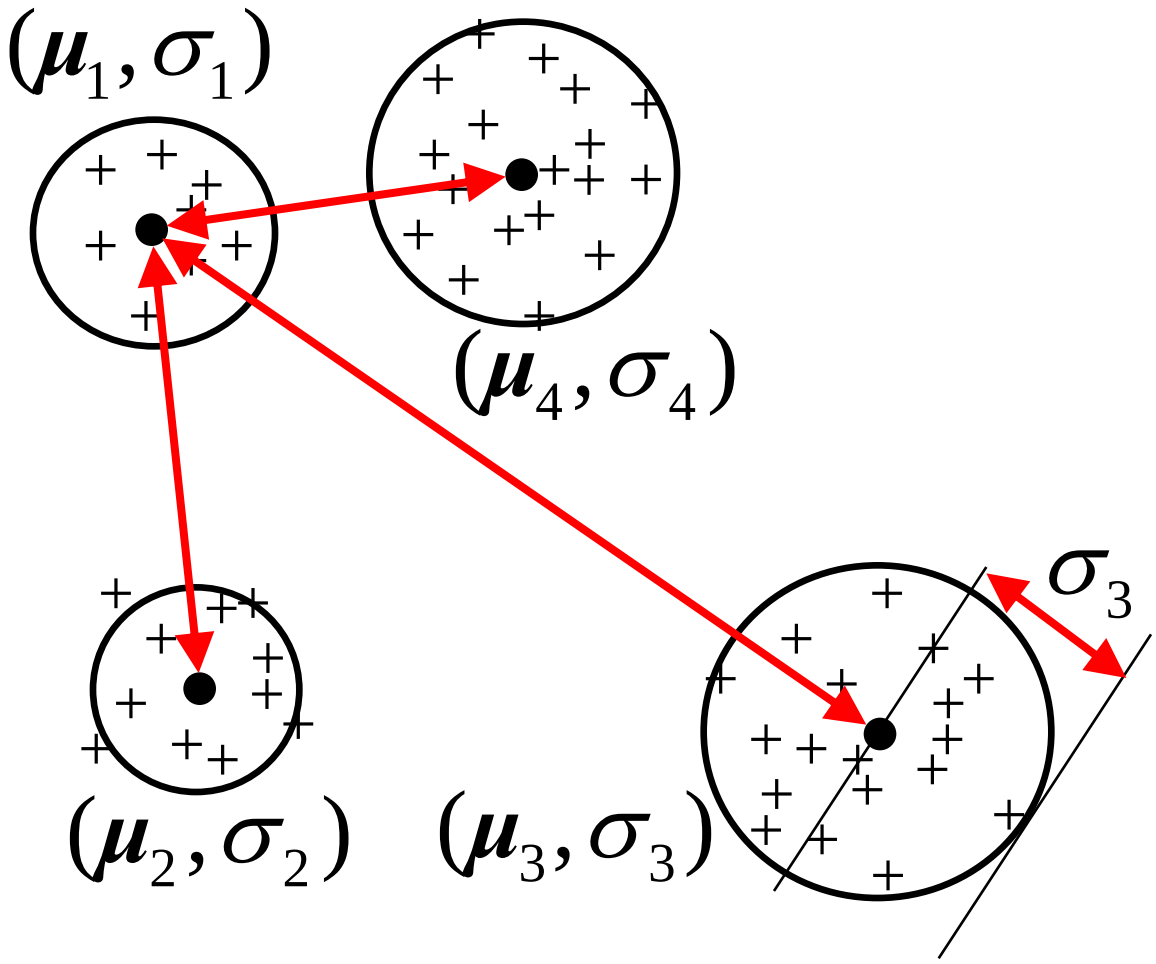
Davies-Bouldin index (2)



$$\sigma_j = \sqrt{\frac{1}{n_j} \sum_{x_i \in C_j} \left\| x_i - \mu_j \right\|^2}$$

$$\mu_j = \frac{1}{n_j} \sum_{x_i \in C_j} x_i$$

Davies-Bouldin index (3)



$$R_{jk} = \frac{\sigma_j + \sigma_k}{\left\| \boldsymbol{\mu}_j - \boldsymbol{\mu}_k \right\|}$$

$$\sigma_j = \sqrt{\frac{1}{n_j} \sum_{\boldsymbol{x}_i \in C_j} \left\| \boldsymbol{x}_i - \boldsymbol{\mu}_j \right\|^2}$$

$$\boldsymbol{\mu}_j = \frac{1}{n_j} \sum_{\boldsymbol{x}_i \in C_j} \boldsymbol{x}_i$$

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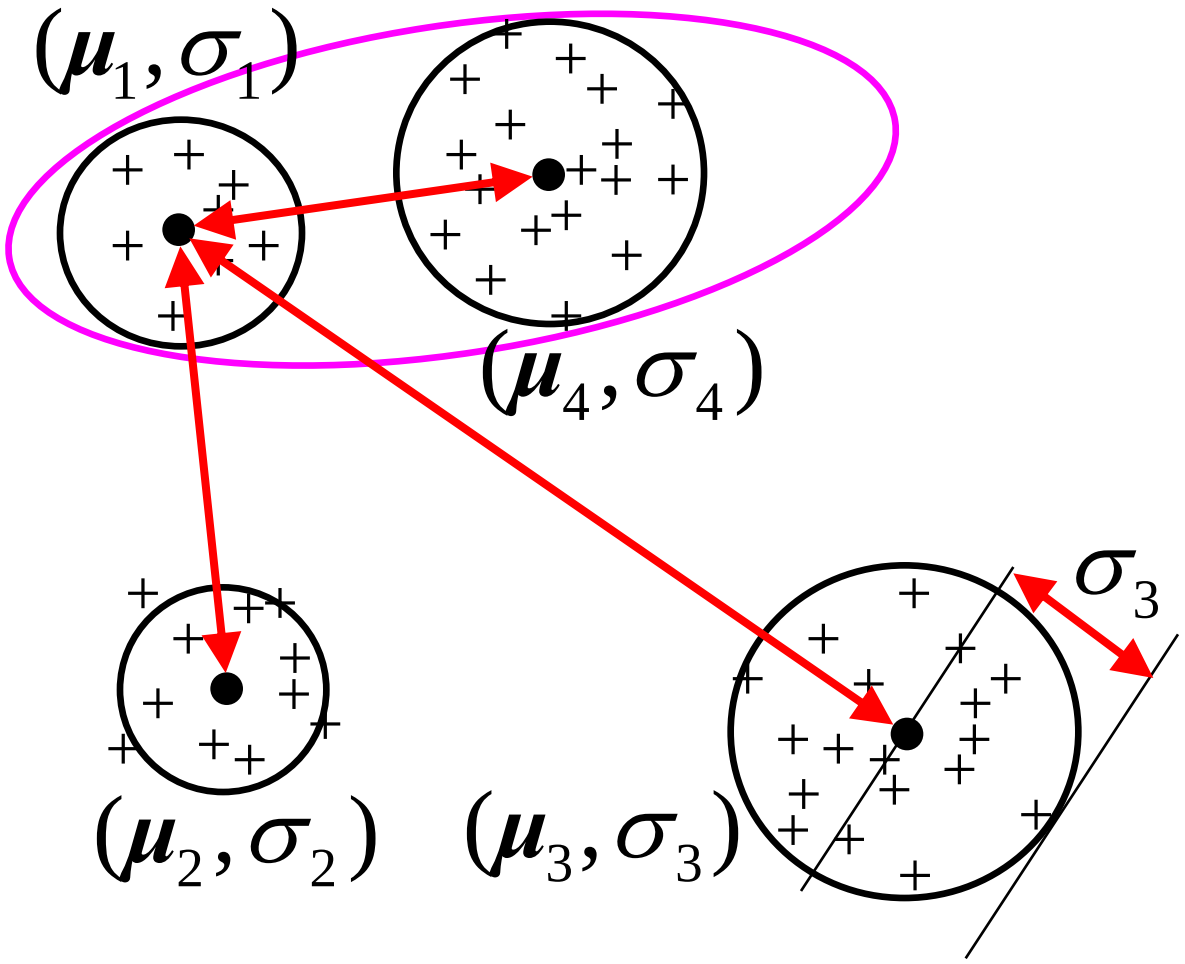
Davies-Bouldin index (4)



$$R_{jk} = \frac{\sigma_j + \sigma_k}{\left\| \boldsymbol{\mu}_j - \boldsymbol{\mu}_k \right\|}$$

$$R_j = \max_{k=1,..g;k\neq j} R_{jk}$$

Davies-Bouldin index (5)

$$R_{jk} = \frac{\sigma_j + \sigma_k}{\left\| \boldsymbol{\mu}_j - \boldsymbol{\mu}_k \right\|}$$

Paired cluster criterion

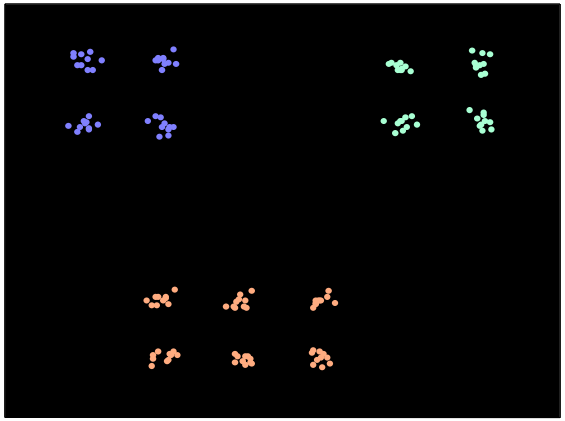
$$R_j = \max_{k=1,..g;k\neq j} R_{jk}$$

Worst-case value per cluster

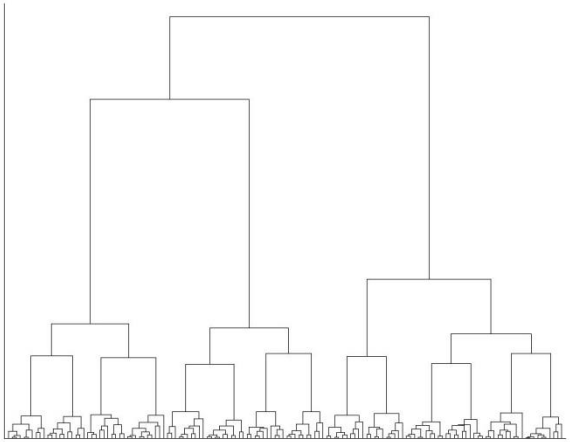
$$I_{DB} = \frac{1}{g} \sum_{j=1}^{g} R_j$$

Average worst-case

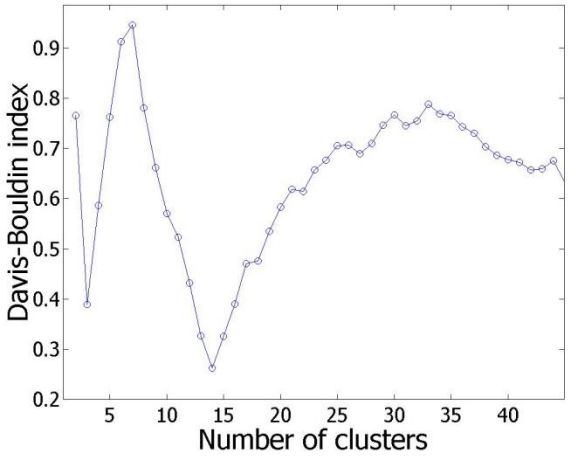
Davies-Bouldin index (5)



Dataset



Complete link



Davies-Bouldin:
3 or 14 clusters

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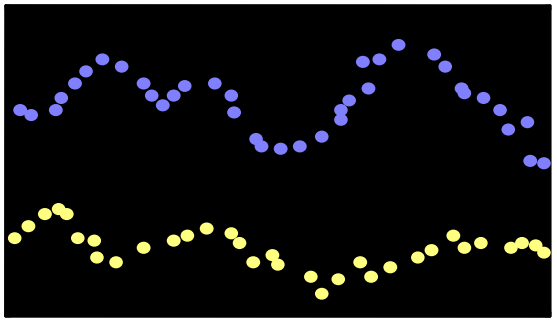
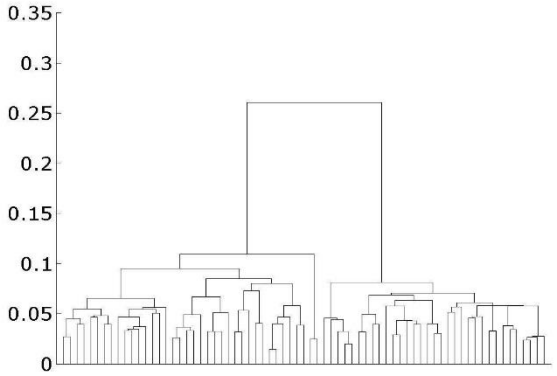
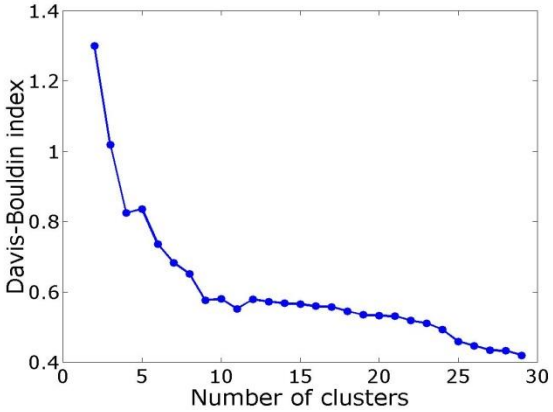
Davies-Bouldin index (7)



Single link

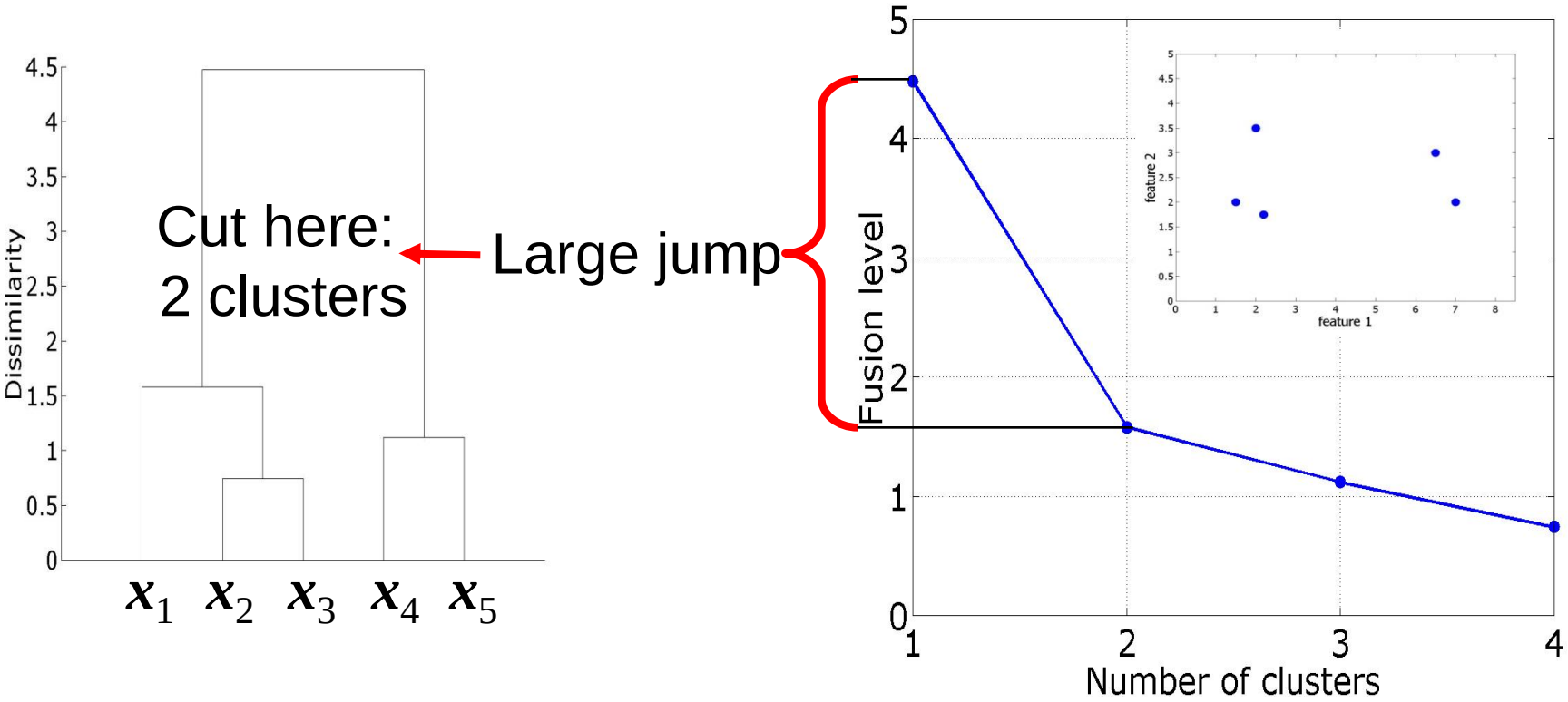


Davies-Bouldin:



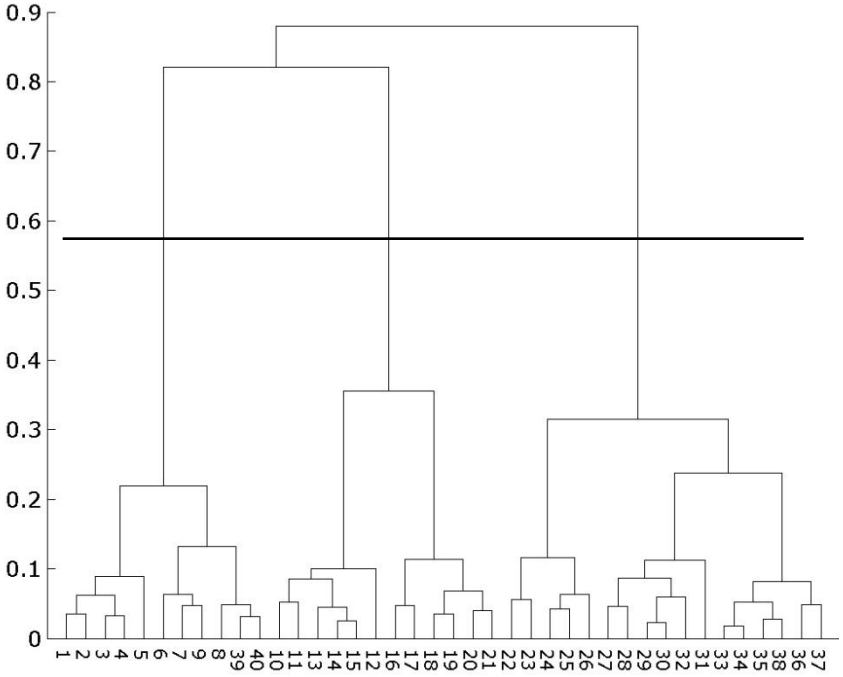
Fusion graph

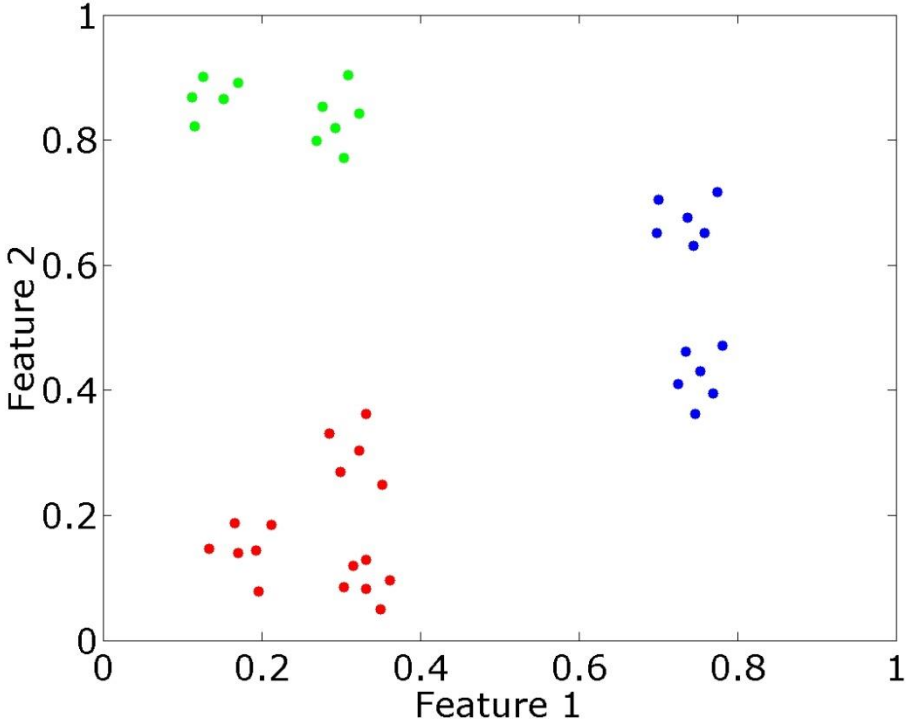
- Heuristic approach: fusion level



Fusion graph (2)

(Euclidean; complete linkage)





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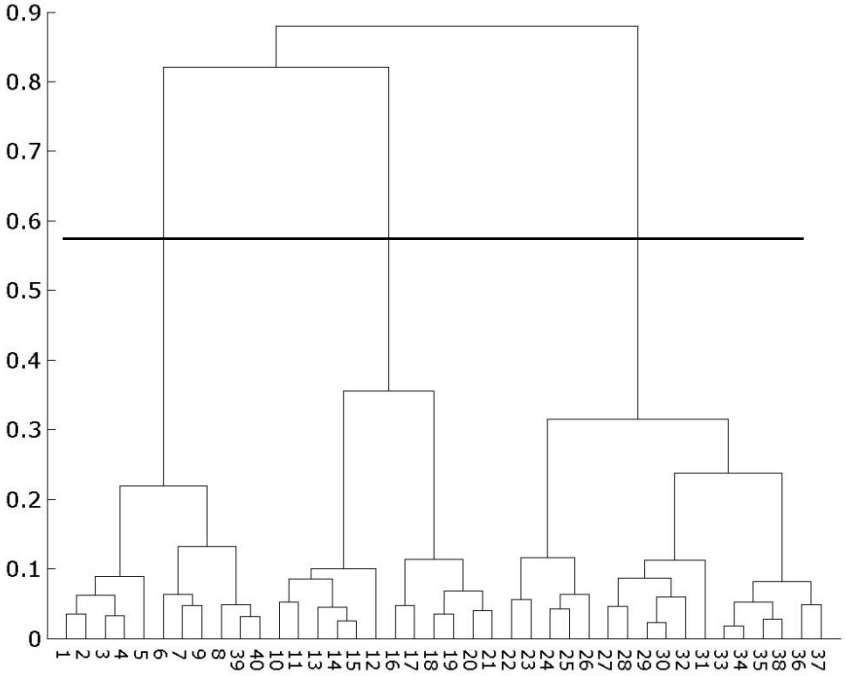
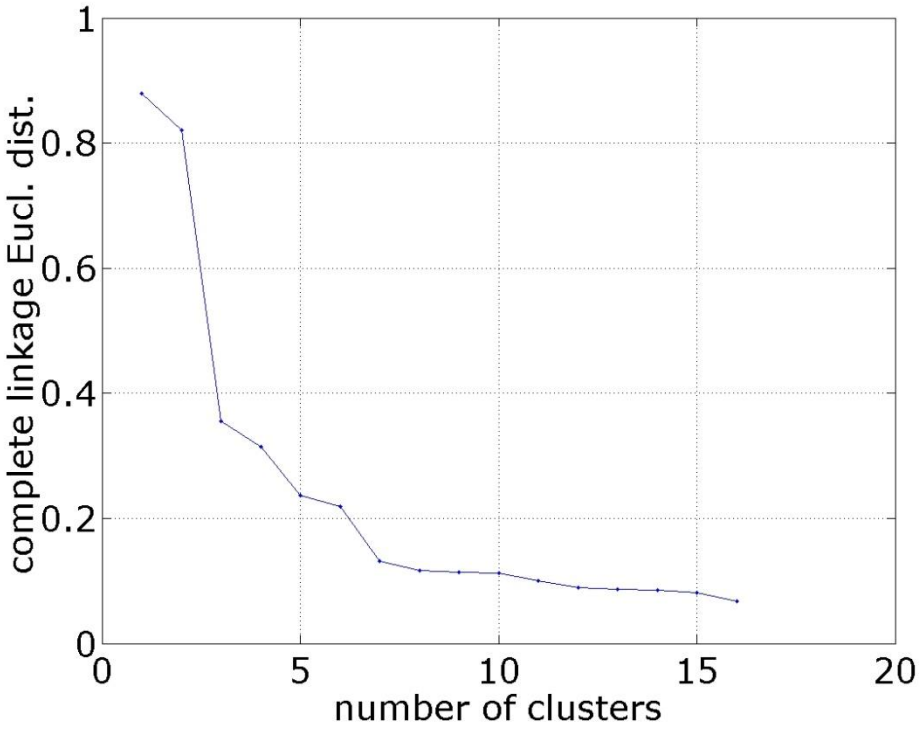
Fusion graph (3)

(Euclidean; complete linkage)





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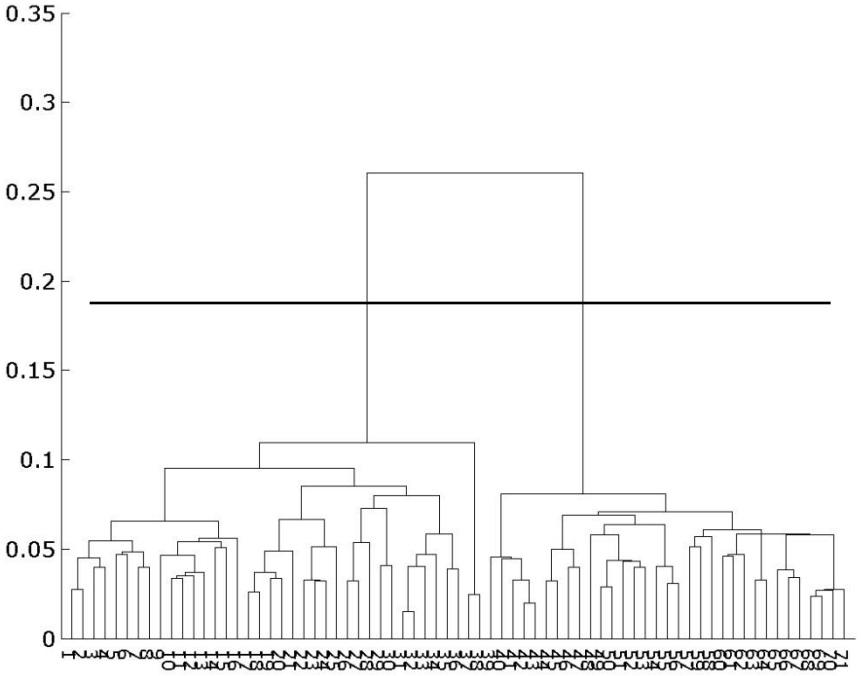
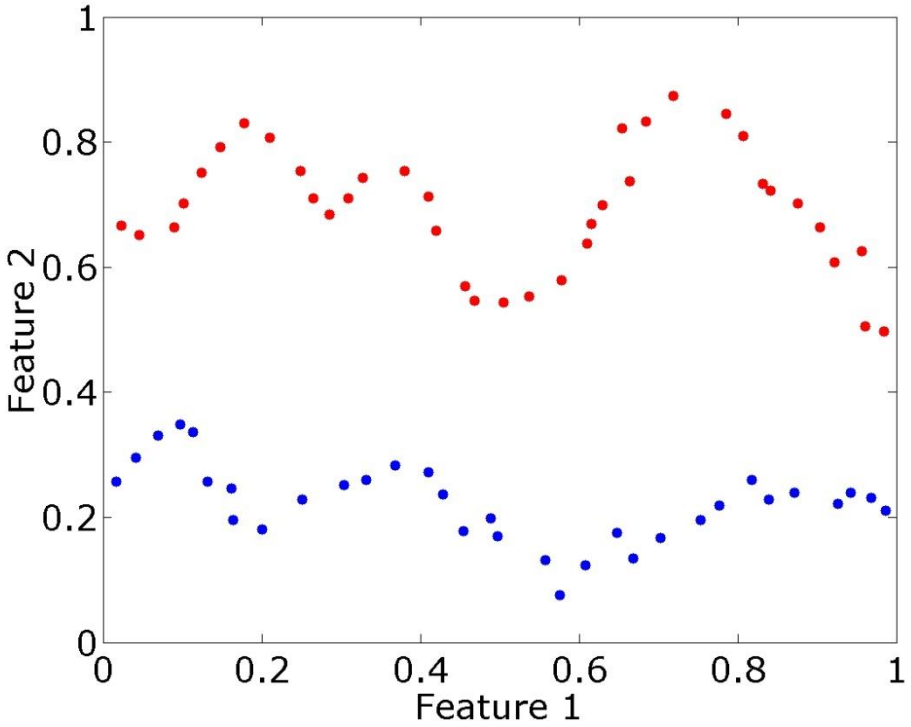
Fusion graph (4)

(Euclidean; single linkage)





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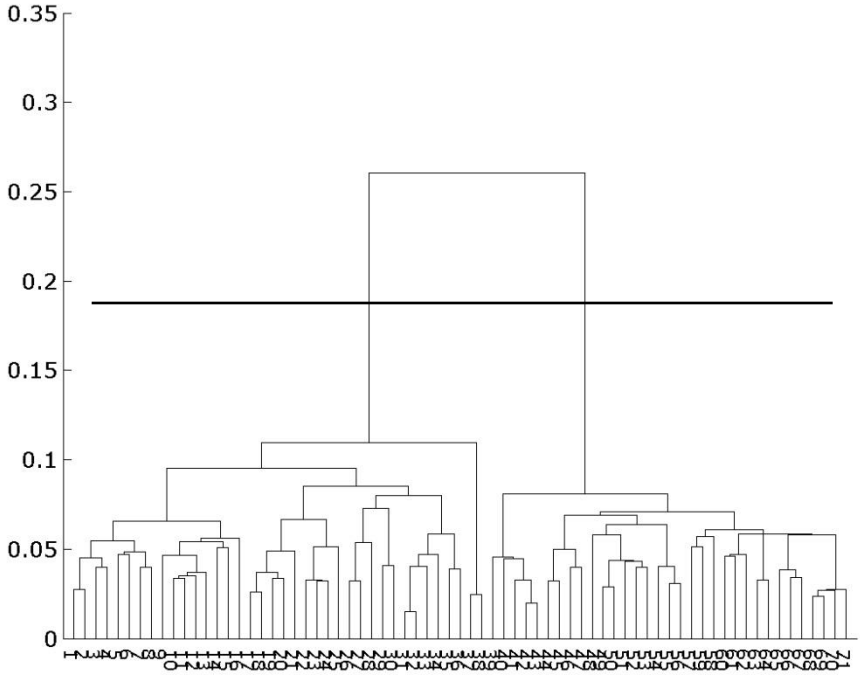
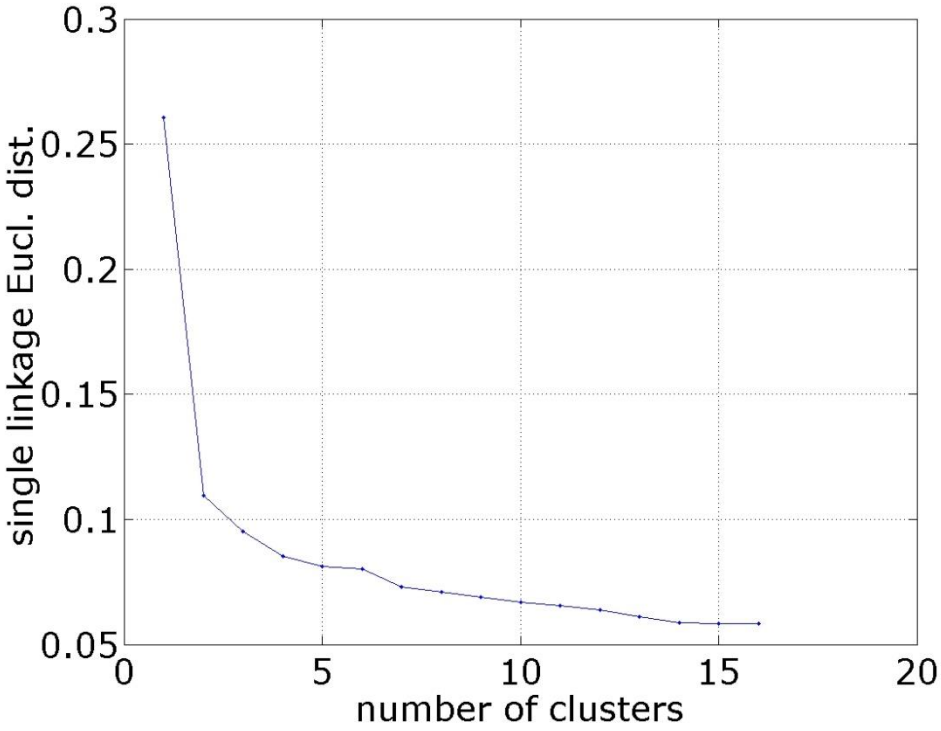
Fusion graph (5)

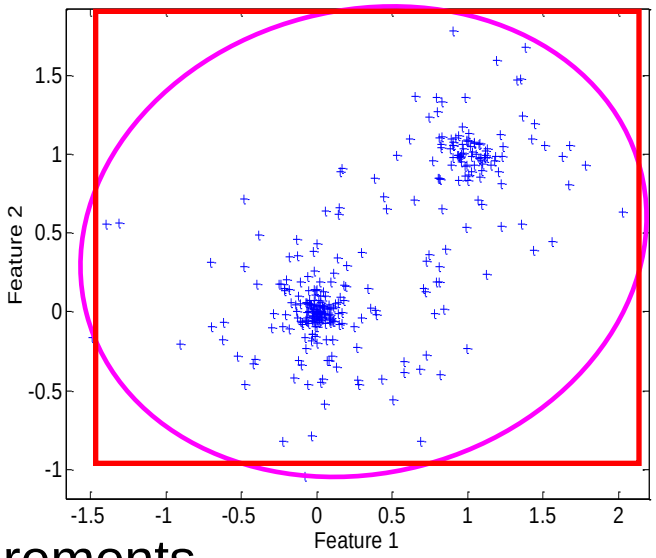
(Euclidean; single linkage)





What is a large jump?

- Compare the fusion graph of the dataset with a *null hypothesis*, i.e. a dataset where the clustering structure has been destroyed
- Different approaches:
  - Generate random data within bounding box or convex hull of data;
  - Preferable to shuffle data, i.e. not generate new data, but perturb relationships between measurements
  - For example, randomly match feature values, i.e. permute values within columns



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The gap statistic

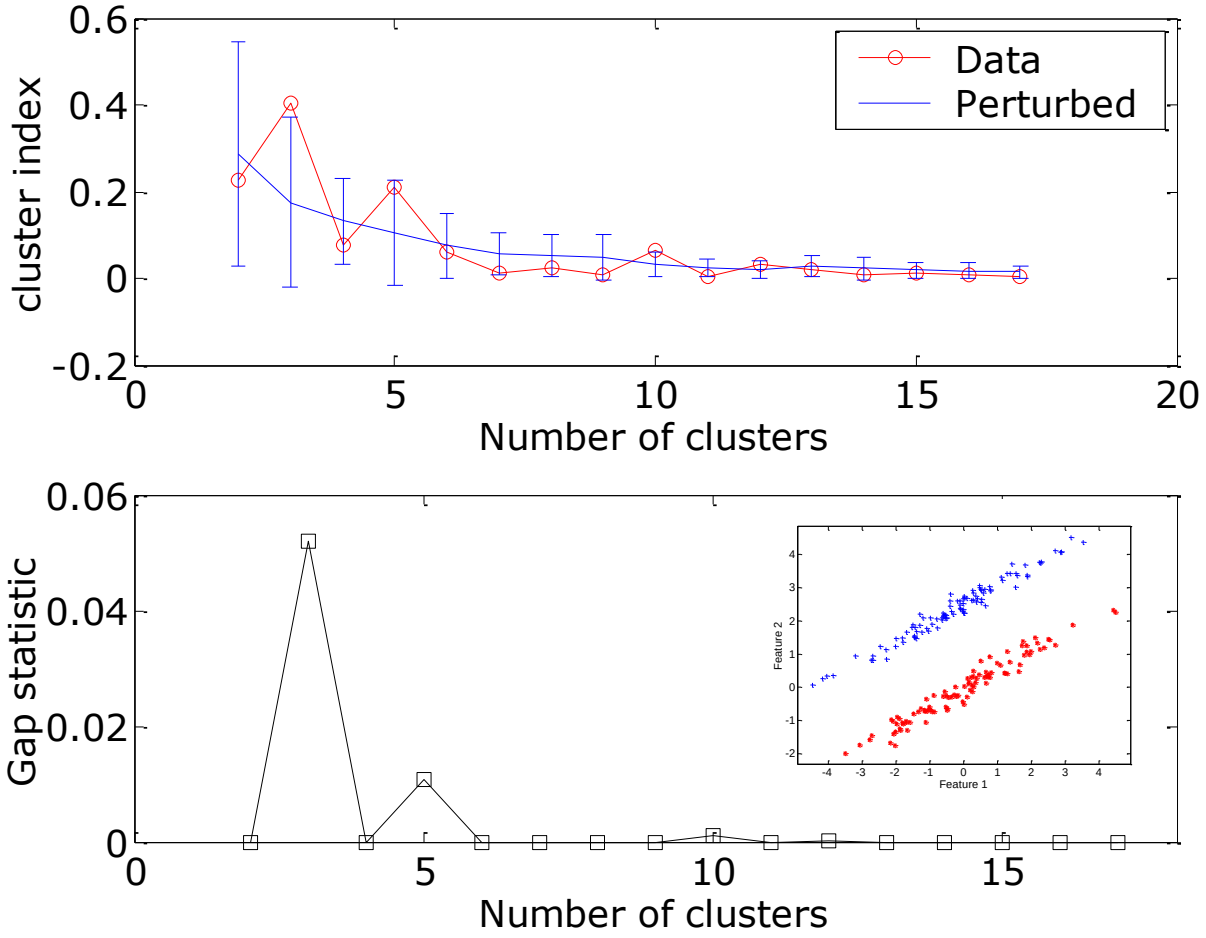
1. Generate dendrogram and extract fusion graph, f_j
2. Repeat r times
   1. Perturb columns
   2. Generate dendrogram and fusion graph, $f^*_{j,r}$
3. Compute average μ^*_j and standard deviation σ^*_j of these perturbed graphs
4. Compute the difference between the data fusion graph and the average perturbed fusion graph (*gap statistic*):

$$g_j^{gap} = \max\left\{ f_j - \mu_j^*, 0 \right\}, j = 1, 2, ..., g$$

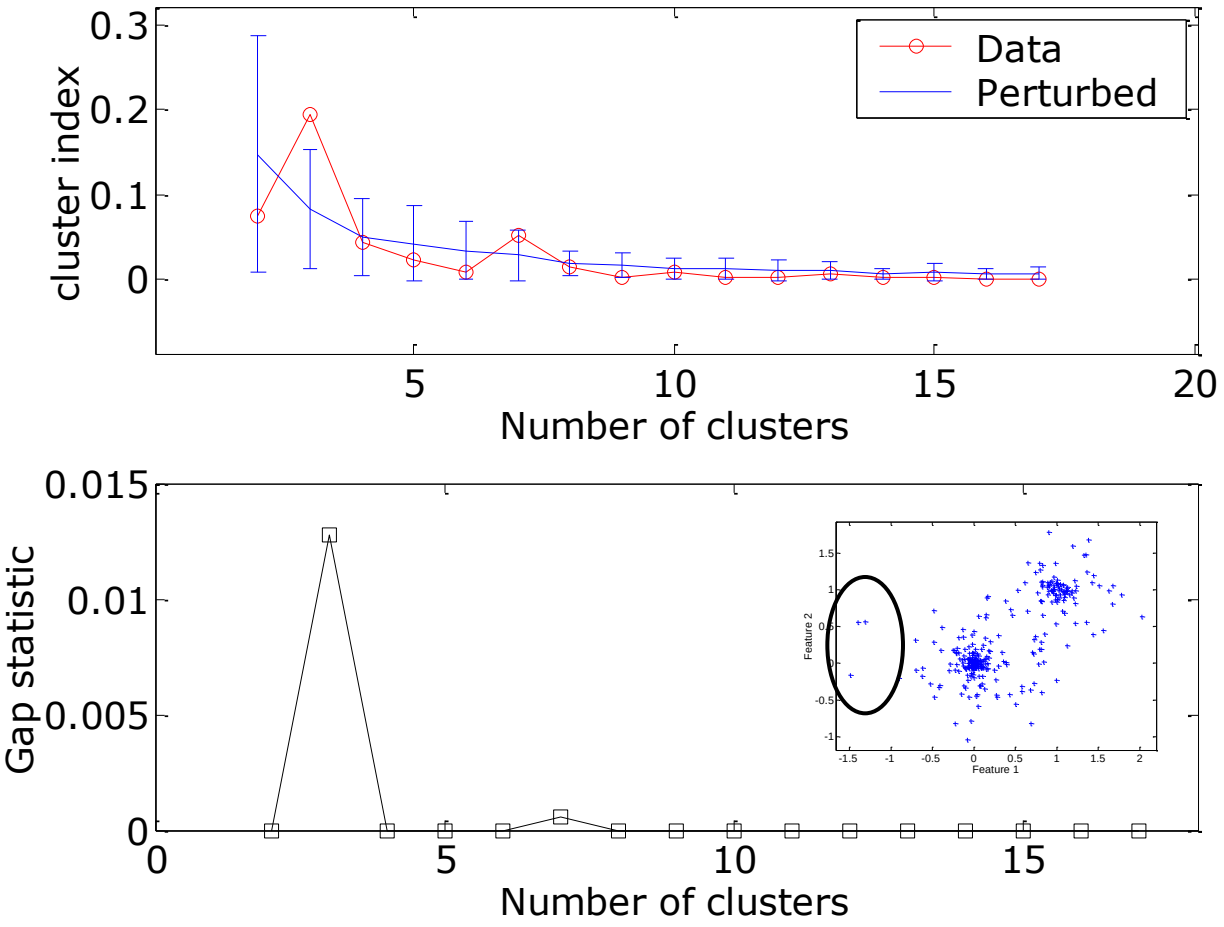
5. Look for large values of gap statistic $g_j^{gap} = f_j$

BioSB

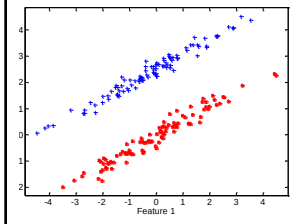
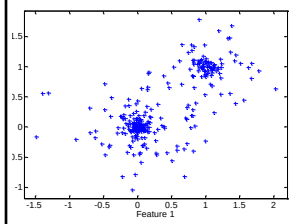
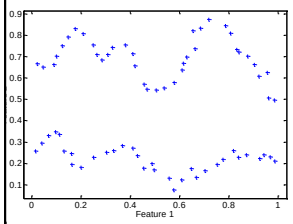
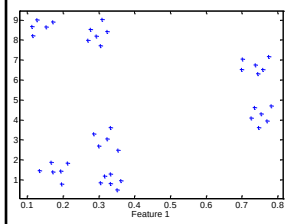
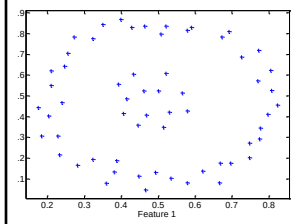
Gap fusion graph (single linkage)



Gap fusion graph (single linkage) (2)



DBI vs. fusion graphs

					
DBI (s)	?	3/4	?	4	4+
DBI (c)	8+	2	5+	4	8+
Gap fusion graph (s)	3	3	2	3	2
Gap fusion graph (c)	2 (?)	2	4	3	3

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Recapitulation

- *Cluster validation* is used for:
  - Assessing clustering
  - Deciding on the number of clusters

- Methods:
  - *Distortion* measures (dendrogram)
  - *Davies-Bouldin index*
  - *Fusion graph* and *gap statistic*

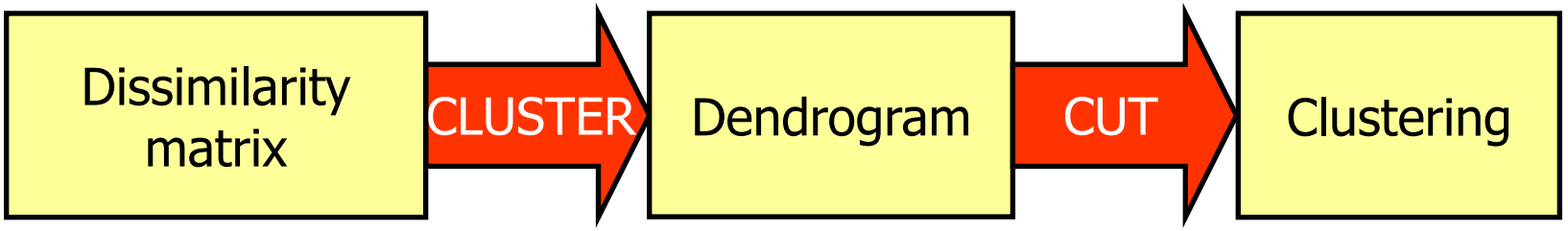
- When applying cluster validation, one also needs to define what a good cluster is – like in clustering itself.
  There's no free lunch...

BioSB

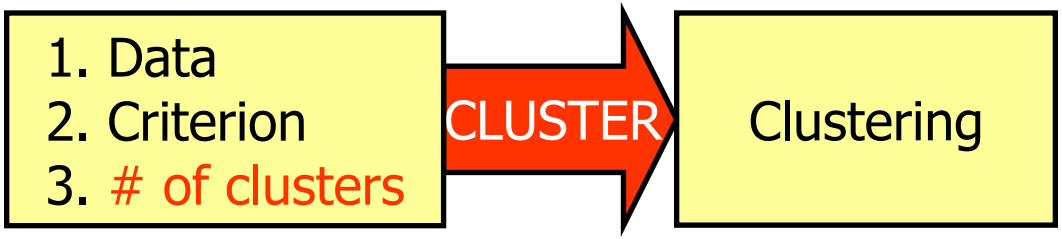
Exercise 2.20-2.28

Clustering overview

1. Hierarchical:



2. K-means:



3. Density-based:

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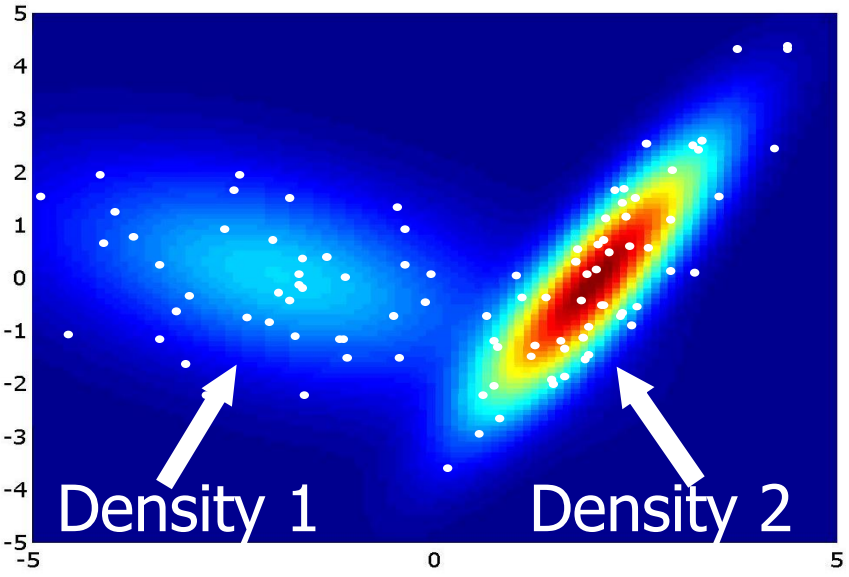
Density-based clustering

- Each cluster is described by a probability density function
- Total dataset described by a *mixture* of density functions
- Clustering = maximizing the mixture fit
- Clusters are based on *a posteriori probabilities*



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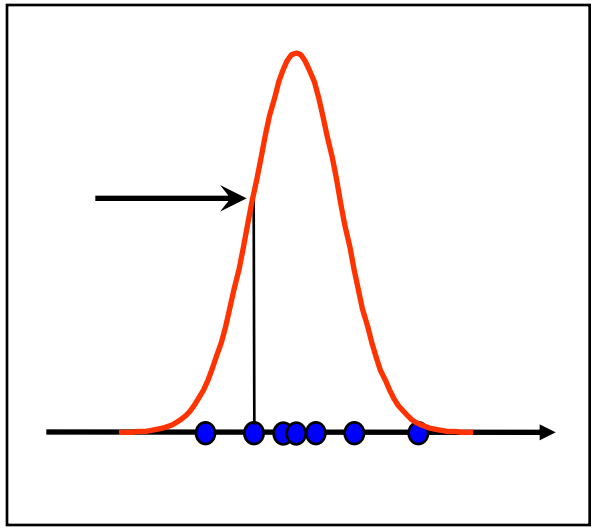
Density-based clustering (2)

- Given:
  - n independent objects: $\{\boldsymbol{x}_1,\ldots,\boldsymbol{x}_n\}$
  - probability density function model:

$$p(\boldsymbol{x} \mid \theta) \sim N(\boldsymbol{\mu}, \boldsymbol{\Sigma})$$



- Estimate parameters $\theta = \{\mu, \Sigma\}$ such that model *fits* data
- Use *likelihood* as criterion: probability of observing the data set, given the model (as on Day 1, for kernel width h in Parzen density estimation)

BioSB

Estimation: maximum likelihood

- General method to estimate parameters θ of probability distribution from data $D = \{x_1, ..., x_n\}$. How?
- Maximize joint probability of the data

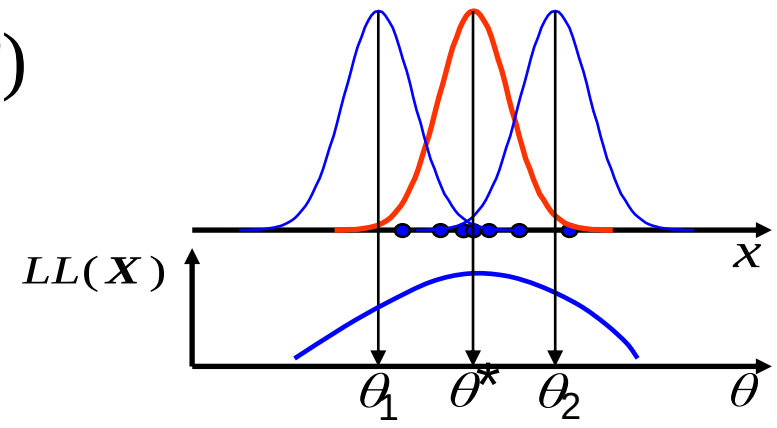
independence

likelihood:

$$L = p(x_1, ..., x_n \mid \theta) = \prod_{i=1}^{n} p(x_i \mid \theta)$$

log-likelihood:

$$LL = \sum_{i=1}^{n} \log \sum_{Q} p(x_i, Q \mid \theta)$$



same solution since log is monotonic

Estimation: maximum likelihood (2)

Two possible outcomes: $x = 0$ or $x = 1$.
Success ($x = 1$) occurs with probability p

Bernoulli distribution: $P(x) = p^x (1-p)^{1-x}$

Likelihood: $P(X_1 = x_1, \ldots, X_n = x_n \mid p) = p^{x_1}(1-p)^{1-x_1} \ldots p^{x_n}(1-p)^{1-x_n}$

$$= p^{n_1}(1-p)^{n-n_1}$$

n_1: # of successes

$$\frac{d(p^{n_1}(1-p)^{n-n_1})}{dp} = 0$$

Maximum at $p = n_1/n$

BioSB

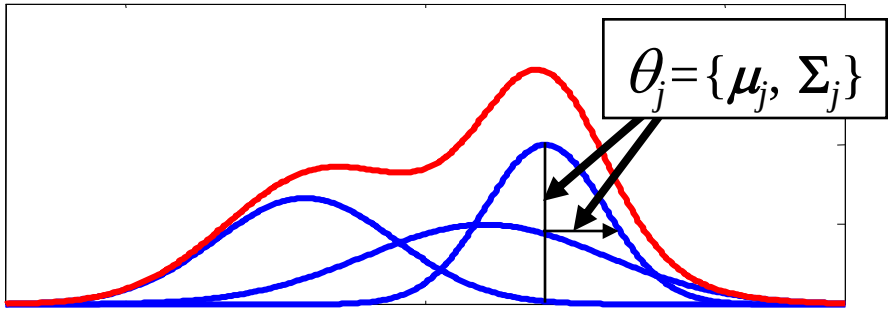
Mixture-of-Gaussians

- Choose Gaussian as component density $p(\boldsymbol{x};\theta_j)$:

$$p(\boldsymbol{x};\theta_j) = \frac{1}{\sqrt{2\pi^p \det(\boldsymbol{\Sigma}_j)}} \exp\left(-\frac{1}{2}(\boldsymbol{x}-\boldsymbol{\mu}_j)^{\mathrm{T}}\boldsymbol{\Sigma}_j^{-1}(\boldsymbol{x}-\boldsymbol{\mu}_j)\right)$$

- Describe complete data set as a mixture of $p(\boldsymbol{x};\theta)$'s:

$$p(\boldsymbol{x};\Psi) = \sum_{j=1}^{g} \pi_j p(\boldsymbol{x};\theta_j) \quad \text{with} \quad \sum_{j=1}^{g} \pi_j = 1$$



BioSB

Mixture-of-Gaussians (2)

$$p(\mathbf{x};\Psi) = \sum_{j=1}^{g} \pi_j p(\mathbf{x};\theta_j) \quad \text{with} \quad \sum_{j=1}^{g} \pi_j = 1$$

- Parameters:
  - Set number of clusters, g
  - Estimate other parameters by maximum-likelihood:

$$\Psi = (\boldsymbol{\pi}, \theta = \{\boldsymbol{\mu}_j, \boldsymbol{\Sigma}_j\}_{j=1\ldots g})$$

mixture coefficients

component density parameters

log-likelihood: $$LL(\boldsymbol{X};\Psi) = \sum_{i=1}^{n} \log \sum_{j=1}^{g} \pi_j p(\mathbf{x}_i;\theta_j)$$

BioSB

EM algorithm

- **Problem:** need to simultaneously estimate two interdependent things...
  - Cluster membership of each object
  - Density parameters of each cluster: $\pi_j, \boldsymbol{\mu}_j, \boldsymbol{\Sigma}_j$

- **Expectation-Maximization algorithm:**
  - General class of algorithms for this type of problem
  - Repeatedly:
    - Recalculate cluster membership of each object *(E)*
    - Recalculate density parameters of each cluster *(M)*

- Introduce a hidden variable *z* to explicitly indicate mixture components

$$\pi_j = p(z = j)$$

BioSB

Intermezzo: probabilities

$n = 20$

	1	2	3	4	5	6
die 1	•	• •	•••	•••	•	•
die 2			•	•	•••	••••

sum rule: $P(x) = \sum_y P(x, y)$

$$1/5 = P(3) = P(3,\ \text{die 1}) + P(3,\ \text{die 2}) = 3/20 + 1/20$$

product rule: $P(x, y) = P(x \mid y)P(y) = P(y \mid x)P(x)$

$$3/20 = P(3,\ \text{die 1}) = P(3 \mid \text{die 1})P(\text{die 1}) = (3/11)(11/20) = 3/20$$

$$= P(\ \text{die 1} \mid 3)P(3) = (3/4)(4/20) = 3/20$$

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Intermezzo: Bayes' theorem

From product rule

$$P(x \mid y)P(y) = P(y \mid x)P(x)$$

$$\textbf{Bayes}: \; P(x \mid y) = \frac{P(y \mid x)P(x)}{P(y)} = \frac{P(y \mid x)P(x)}{\sum_x P(y \mid x)P(x)}$$

$$P(\text{die 1} \mid \ 3) = \frac{P(3 \mid \text{die 1})P(\text{die 1})}{P(3)} = \frac{(3/11)(11/20)}{4/20} = 3/4$$

BioSB

EM algorithm (2)

arbitrary distribution hidden variable

$$\log p(D) = \sum_x \log p(x) = \sum_x \sum_z q(z) \log p(x)$$

$$= \sum_{x,z} q(z) \log \frac{p(x,z)}{p(z \mid x)} = \sum_{x,z} q(z) \log \left(\frac{p(x,z)}{p(z \mid x)} \times \frac{q(z)}{q(z)} \right)$$

$$= \sum_{x,z} q(z) \log \left(\frac{p(x,z)}{q(z)} \right) + \sum_{x,z} q(z) \log \left(\frac{q(z)}{p(z \mid x)} \right)$$

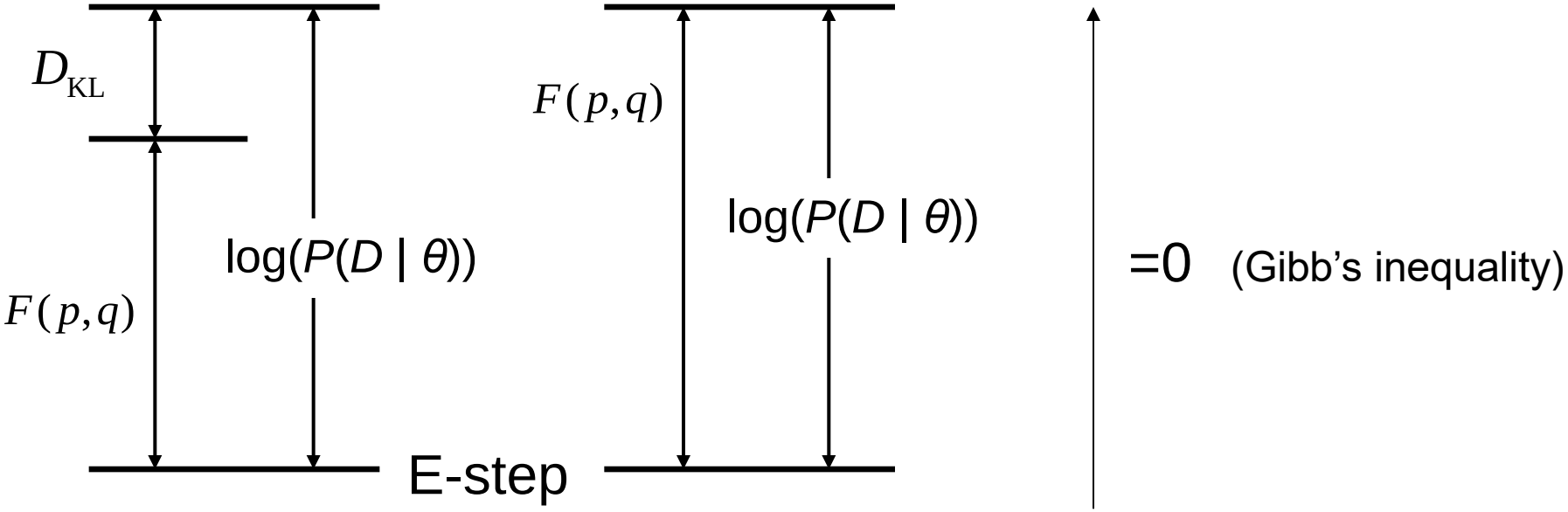
$$= F(p_{\text{joint}}, q) + D_{KL}(q \,\|\, p_{\text{post}})$$

free energy relative entropy (≥ 0)

BioSB

EM algorithm: E-step

$$\log p(D) = \sum_{x,z} q(z) \log \left(\frac{p(x,z)}{q(z)} \right) + \boxed{\sum_{x,z} q(z) \log \left(\frac{q(z)}{p(z \mid x)} \right)}$$



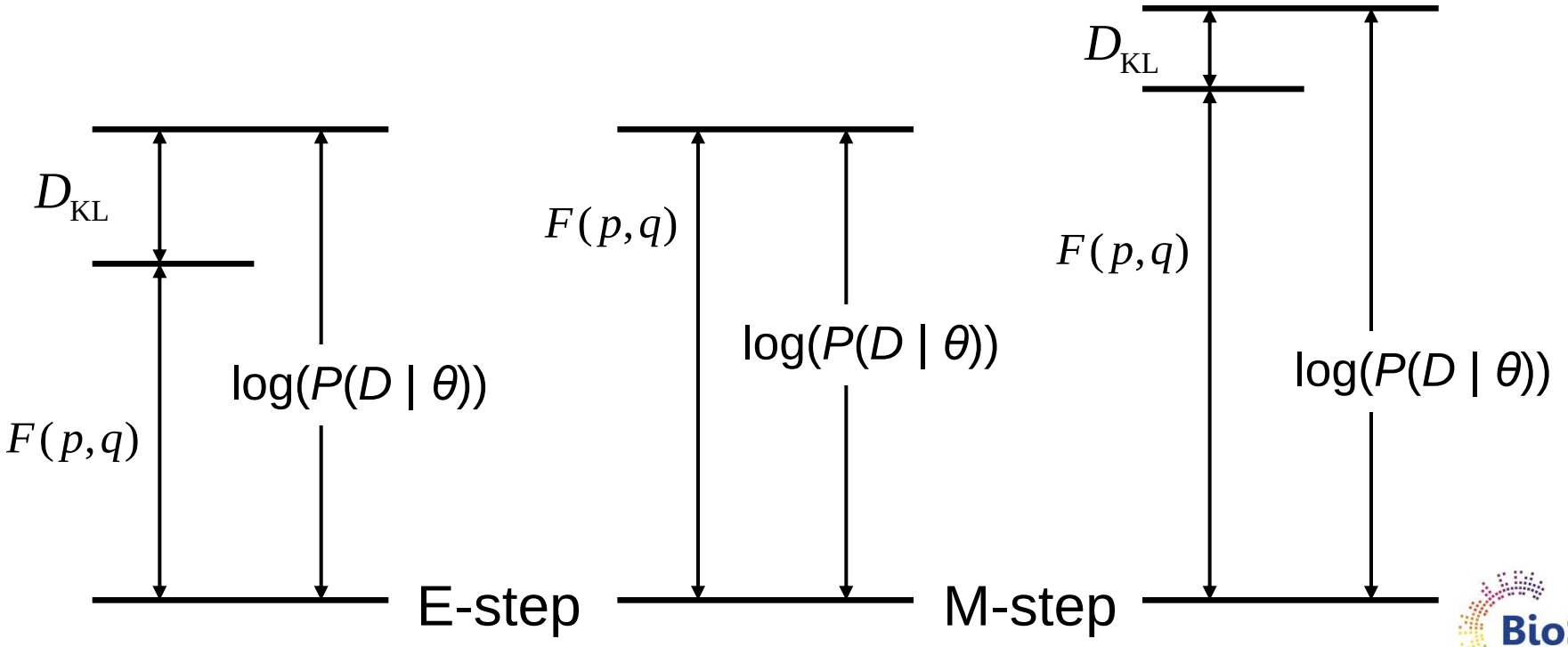
E-step: $q^{\mathrm{new}}(z \mid x) = p_{\mathrm{post}} = p(z \mid x)$

BioSB

EM algorithm: M-step

$$\log p(D) = \sum_{x,z} p(z \mid x) \log \left(\frac{p(x,z)}{p(z \mid x)} \right)$$

M-step: maximize log[$p(D)$] with respect to the parameters



EM algorithm (3)

Iterate to maximize likelihood:

E-step: $p_{\text{post}} = p(z \mid x, \theta)$

Calculate the distribution of the hidden variables given the data and the model parameters

M-step: $\theta^{new} = \arg\max_{\theta} \sum_{x,z} p(z \mid x) \log p(x, z \mid \theta)$

Maximize the expected (with respect to hidden variables) log-likelihood of the complete data.

Compare M-step with MoG log-likelihood: $\sum_{i=1}^{n} \log \sum_{j=1}^{g} \pi_j \, p(\mathbf{x}_i; \theta_j)$

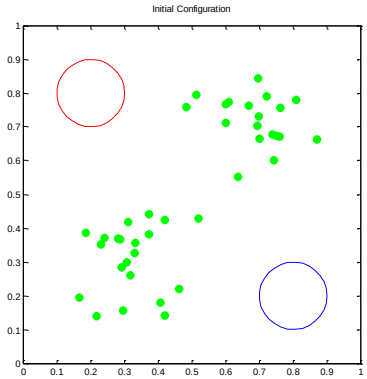
M-step is easier: log within sum

BioSB

EM: mixture model

Very simple example of a model with hidden variables:

2-component mixture model



$$p(x) = \pi_1 p_1(x \mid \theta) + \pi_2 p_2(x \mid \theta)$$

hidden variable z = 1,2 - component label

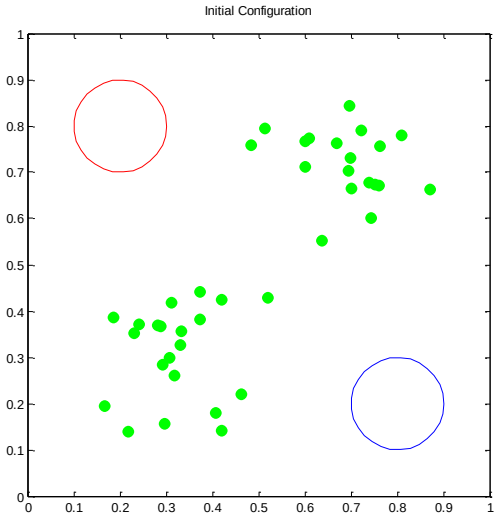
E-step: $p(z = j \mid x, \theta) = \dfrac{p(z = j \mid \theta)\, p(x \mid z = j, \theta)}{p(x \mid \theta)} = \dfrac{\pi_j p_j(x \mid \theta)}{p(x)}$

responsibility

M-step: maximize $\sum_{x, z \in \{1,2\}} p(z \mid x) \log p(x, z \mid \theta)$

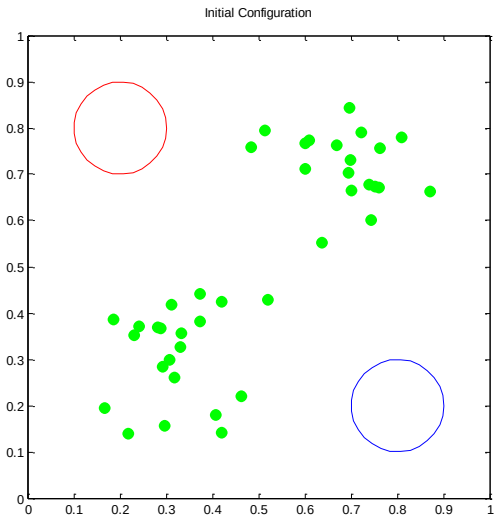
BioSB

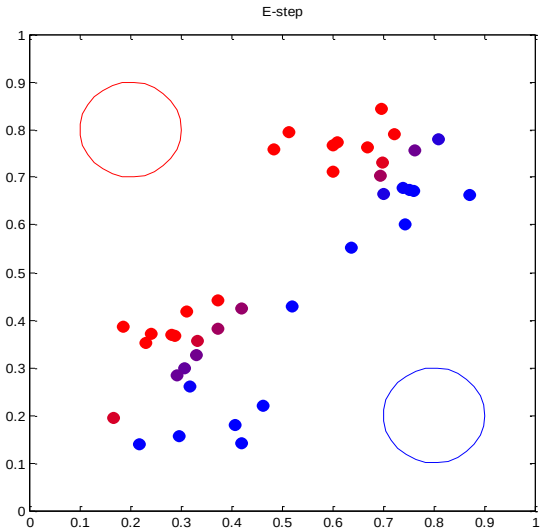
EM: mixture model (2)



Initialization

EM: mixture model (3)





Initialization

E-step

BioSB

EM: mixture model (4)

- **M-step**: Maximization

  Maximize the expected complete LL by updating

  - mixture coefficients π_j
  - cluster means and covariances $\theta_j=\{\mu_j, \Sigma_j\}$, $j=1,\ldots,g$:

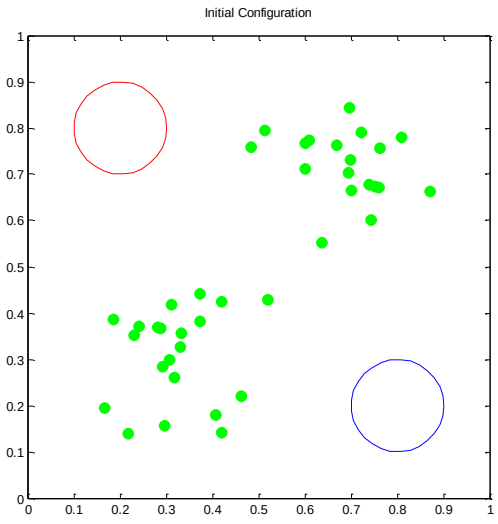
$$\hat{\pi}_j = \frac{1}{n}\sum_{i=1}^{n} p(z=j \mid x_i) = \frac{1}{n}\sum_{i=1}^{n} w_{ij}$$ } "total membership"

$$\hat{\mu}_j = \frac{\sum_{i=1}^{n} w_{ij}\boldsymbol{x}_i}{\sum_{i=1}^{n} w_{ij}}$$

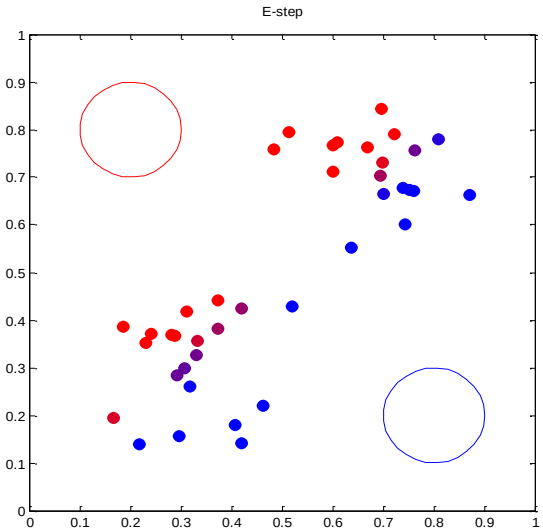
$$\hat{\Sigma}_j = \frac{\sum_{i=1}^{n} w_{ij}(\boldsymbol{x}_i - \hat{\mu}_j)(\boldsymbol{x}_i - \hat{\mu}_j)^T}{\sum_{i=1}^{n} w_{ij}}$$ } weighted sums

BioSB

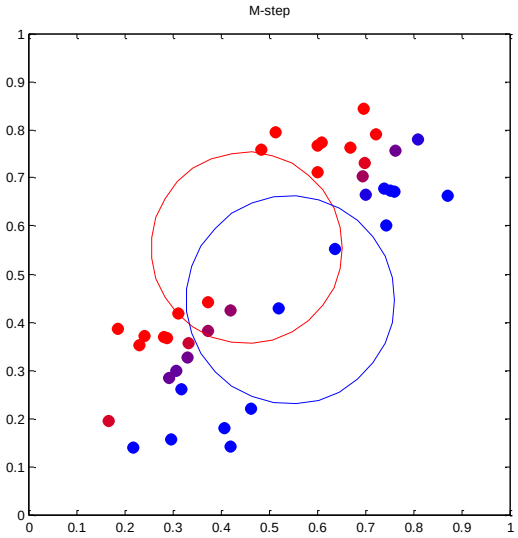
EM: mixture model (5)



Initialization

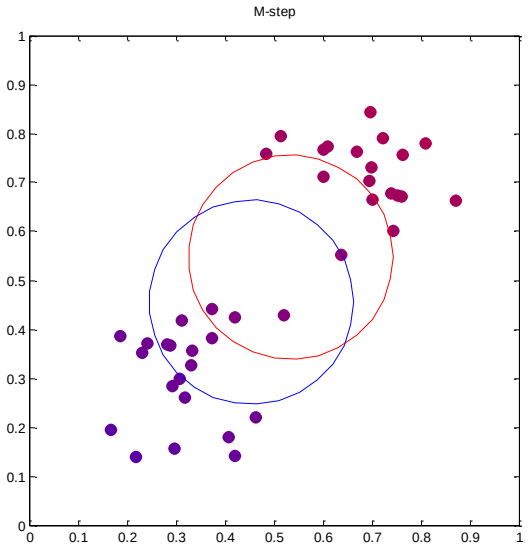


E-step



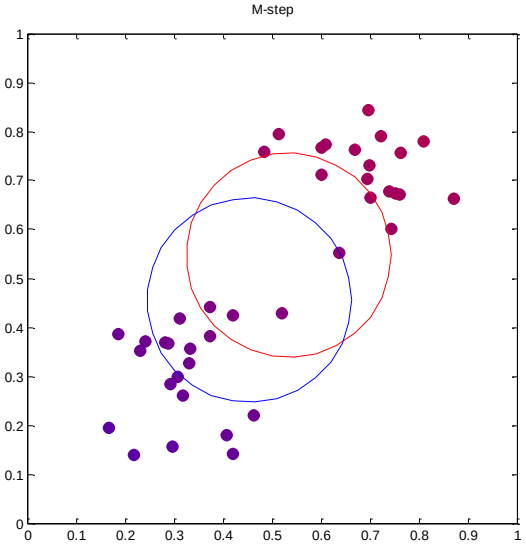
M-step

EM: mixture model (6)

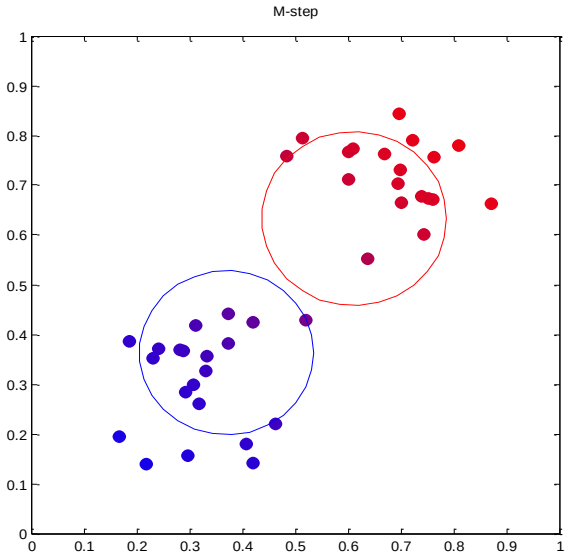


M-step: 3

EM: mixture model (7)



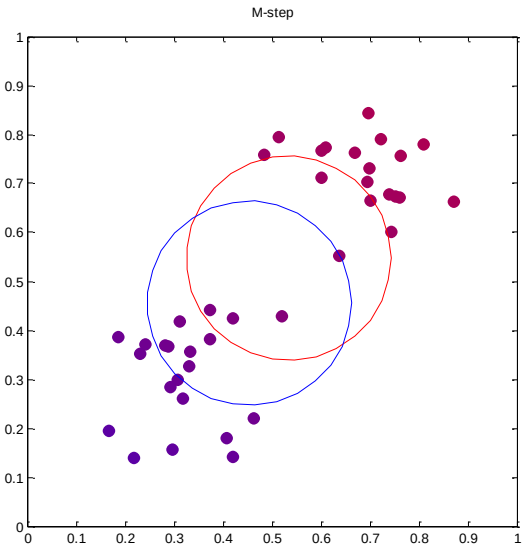
M-step: 3



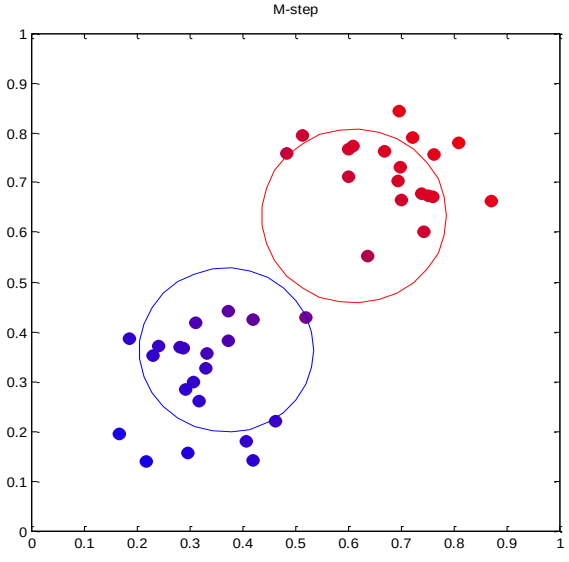
M-step: 5

BioSB

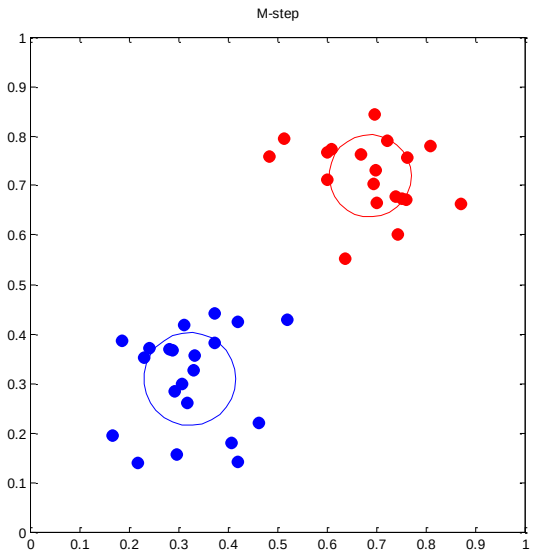
EM: mixture model (8)



M-step: 3



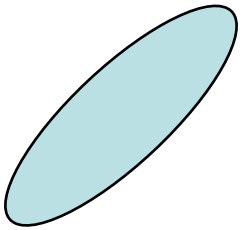
M-step: 5



M-step: 9

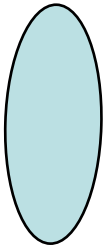
Mixture-of-Gaussians (3)

- ‘Gauss’:



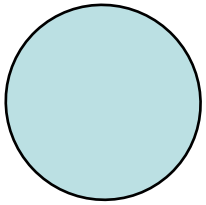
$$\boldsymbol{\Sigma} = \begin{bmatrix} \sigma_{11} & \sigma_{12} \\ \sigma_{21} & \sigma_{22} \end{bmatrix}$$

- ‘Aligned’:



$$\boldsymbol{\Sigma} = \begin{bmatrix} \sigma_{11} & 0 \\ 0 & \sigma_{22} \end{bmatrix}$$

- ‘Circular’:



$$\boldsymbol{\Sigma} = \begin{bmatrix} \sigma & 0 \\ 0 & \sigma \end{bmatrix}$$

BioSB

EM: mixture model (9)

- If...
  - all clusters are spherical
  - the variance of each cluster is infinitely small

$$\boldsymbol{\Sigma} = \begin{bmatrix} \varepsilon^2 & 0 & 0 \\ 0 & \varepsilon^2 & 0 \\ 0 & 0 & \varepsilon^2 \end{bmatrix}, \qquad \varepsilon \to 0$$

then the EM algorithm simplifies to the *K*-means algorithm (samples are always assigned to the closest cluster!)

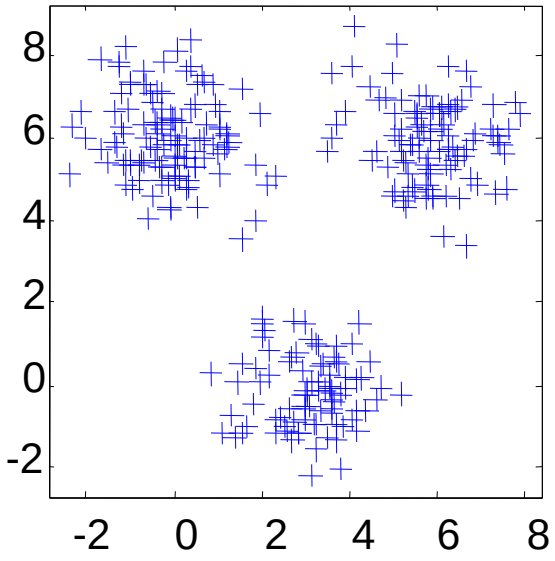
BioSB

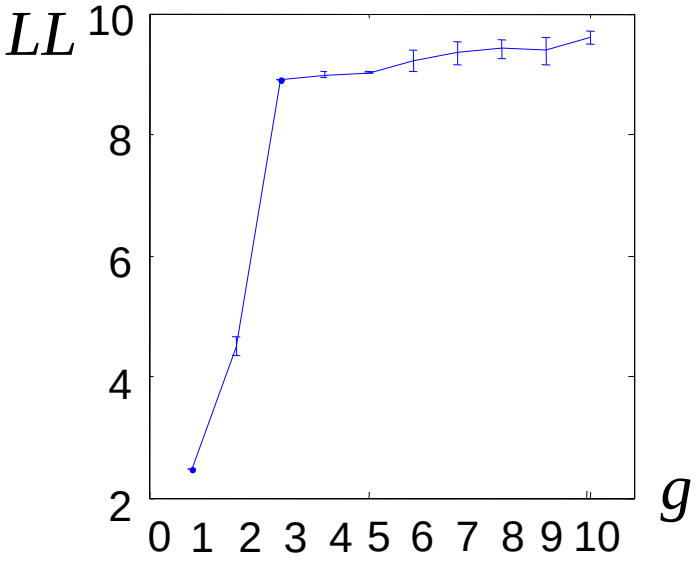
EM algorithm (4)

- Disadvantages:
  - can get stuck in local minima
  - depends on initial conditions
  - convergence can be slow
  - problems with covariance estimates:
    if too few samples are members of a cluster,
    there will not be enough data to base estimate on
- Advantages:
  - simple to implement

Cluster validation: log-likelihood

- For probabilistic models (e.g. mixture-of-Gaussians):
  - Log-likelihood will probably not increase anymore when too many clusters are used
  - Look for “plateau” in log-likelihood graph





- Problem: when $g = n$, the log-likelihood is infinite;

  Solution: information criteria (Day 4)

Recapitulation

- Density based clustering:
  - Assume a *probability density function* per cluster
  - Train using the *EM algorithm*

- Example:
  - *Mixture of Gaussians*
  - But many probability densities fit in the same framework principal component analysis, factor analysis, …

- EM algorithm:
  - problem *decomposition*: simple to implement
  - sensitive to *local minima*

BioSB

Exercise 2.29