Machine Learning for Bioinformatics & Systems Biology

1. Introduction & density estimation

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Perry Moerland *Amsterdam UMC, University of Amsterdam*
Lodewyk Wessels *Netherlands Cancer Institute*

Some material courtesy of Robert Duin, David Tax & Dick de Ridder

Programme

Day	Lecturer	Subjects
Monday 26/9	Marcel Reinders	Introduction to machine learning Bayesian framework Density estimation Bayesian classification
Tuesday 27/9	Perry Moerland	Parametric classifiers Nonparametric classifiers Discriminant analysis Decision trees & random forests
Wednesday 28/9	Lodewyk Wessels	Feature selection Sparse classifiers Feature extraction Embeddings
Thursday 29/9	Perry Moerland	Hierarchical clustering Agglomerative clustering Model-based clustering Hidden Markov models
Friday 30/9	Marcel Reinders	Artificial neural networks Support vector machines Classifier ensembles Complexity

Schedule

When	What	Where
9.00-12.00	Lecture	AMC/HvA
12.00-13.00	Lunch break	The Box (G0-114)
13.00-17.00	Computer lab	AMC/HvA

- Coffee/tea etc. and lunch will be provided
- Wednesday there will be drinks and bites at 17.00 in Grand-Café ZO (at 5 minutes walking distance from the AMC)


K01-222-1: basement

Certificates and examination

- To obtain a certificate of successful completion:
  - Analyse a biological dataset (preferably one from your own practice) using the tools provided in the course
  - Write a short report (5-10 pages) on the results
  - Hand this in no later than **October 21, 2022 (3 weeks after end of course)**
- If you have no dataset available, one will be provided
- Grade will be “pass” or “fail”, with at most one resubmission
- If no report or “fail”: certificate of attendance

BioSB: The Netherlands Bioinformatics and Systems Biology research school

- Yearly conference: 9-10 May 2023

- Courses:
  - Algorithms for Genomics, Delft, 10-14 October 2022
  - Computational Metagenomics, Wageningen, 10-12 October 2022
  - Single cell Analysis, Leiden,10-14 October 2022
  - Integrated modeling and optimization, 12-16 December 2022
  - Constraint-based modeling, 13-17 February 2023

- YoungCB: Regional Student Group (RSG) Netherlands of the International Society of Computational Biology

Course

Modelling …. Learning from examples

Machine learning

- Wikipedia:
  - "the scientific study of **algorithms** and **statistical models** that computer systems use to perform a specific task without using explicit instructions, relying on **patterns** and **inference** instead … Machine learning algorithms build a **mathematical model** based on **sample data**, known as "**training data**", in order to make **predictions** or **decisions** without being explicitly programmed to perform the task.“
- Christopher M. Bishop:
  - "**Pattern recognition** has its origins in **engineering**, whereas **machine learning** grew out of **computer science**. However, these … can be viewed a two facets of the **same field**"

Machine learning (2)

- The construction of **approximate, generalizing (predictive) models** by **learning from examples**, for problems for which *no full physical model is known* (yet)
- Focus in this course will be on **classification** and **statistical machine learning**, not (so much) on *regression, structural/syntactic* pattern recognition and *reinforcement learning*.

- Related areas
  - Applied statistics
  - Pattern recognition
  - Artificial intelligence
  - Computer vision
  - Data mining

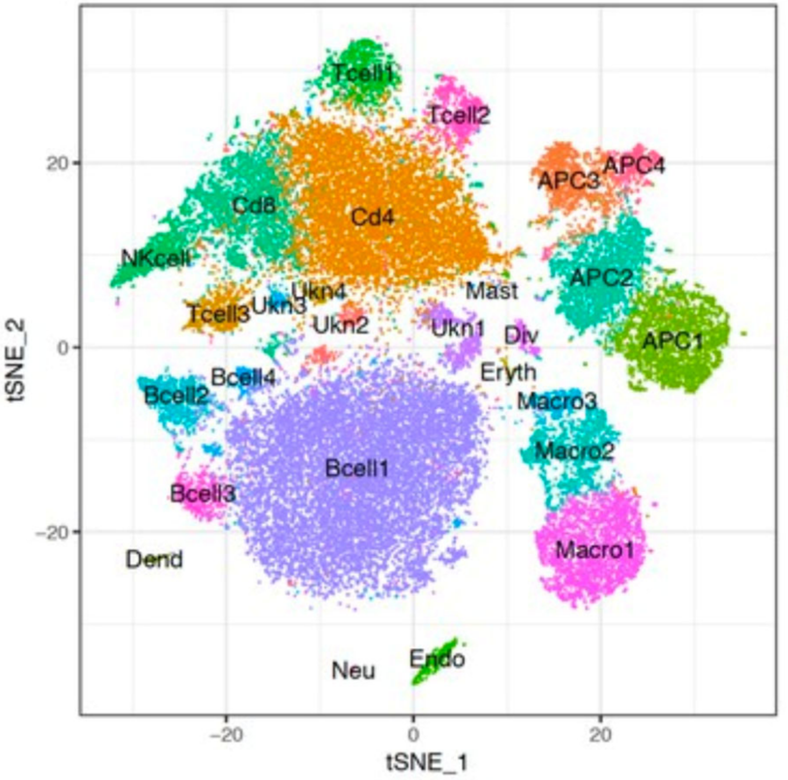
Face recognition, no physical model

Machine learning (3)

- Examples:
  - Computer vision: license plate reading, people counting, face detection, smart cameras, ...
  - Signal processing: thermostat, speech/speaker recognition, ...
  - Information retrieval: Google, Amazon, automated translation, ...
  - Biometrics: fingerprint recognition, iris scan, signature verification...
  - Defensive: friend-or-foe recognition, target tracking, ...
  - Medicine: interpreting scans, diagnostic systems, ...

Machine learning (4)

- Bioinformatics:
  - Gene (function) prediction, SNP prioritization, …
  - Diagnosis/prognosis, biomarker discovery, …
  - Network inference: PPI, metabolic networks, …
  - Cell-type identification, …
  - Etc.



Goal

- After having followed this course, the student has a good understanding of a wide range of machine learning techniques and is able to recognize what method is most applicable to data analysis problems (s)he encounters in bioinformatics and systems biology applications.
- Many problems are in fact machine learning problems!

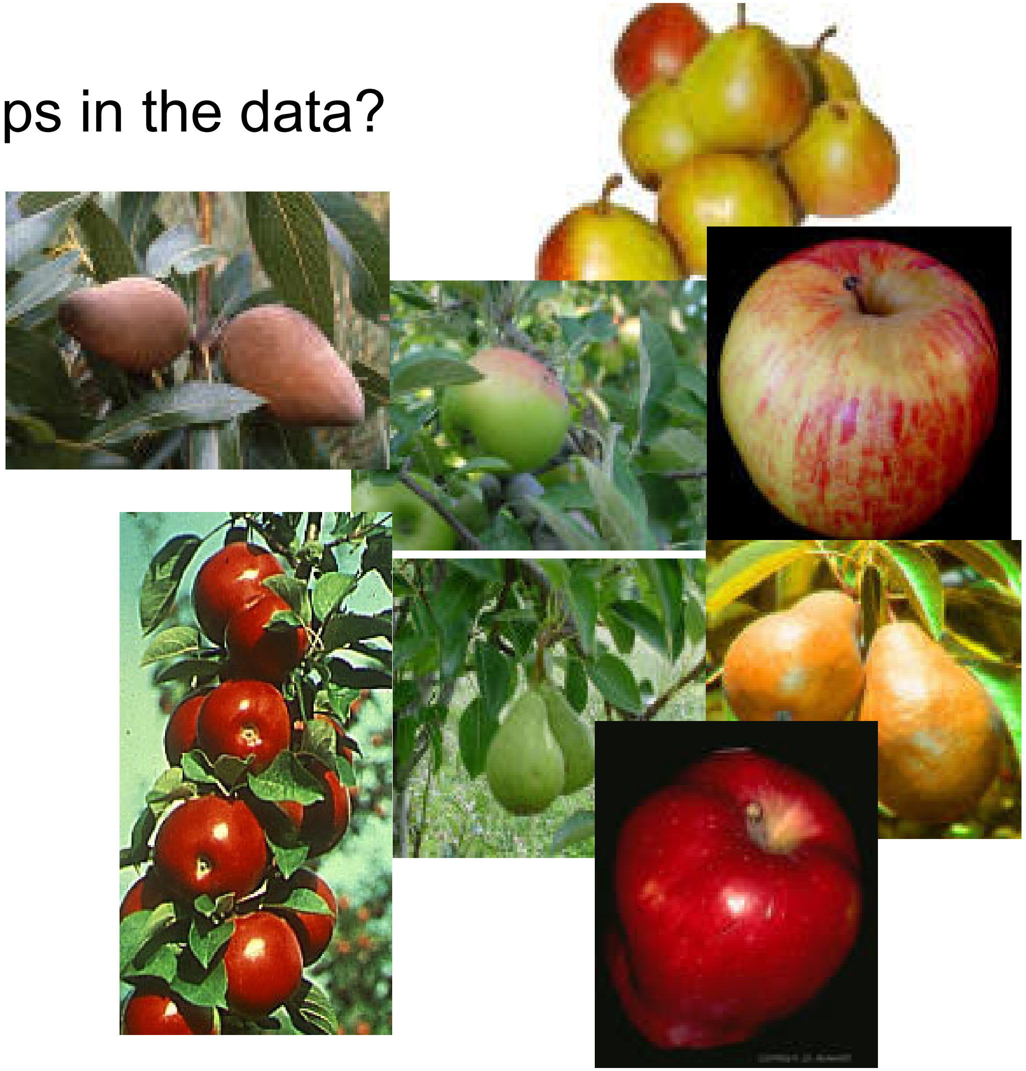
Machine learning (5)

- Finding structure in data
  - Outlier/anomaly detection
  - Clustering
  - Dimensionality reduction,
    selecting useful (combinations of) features
  - Regression
  - Classification
  - ...

- All aimed at *generalisation*:
  making a prediction for data you have not yet seen

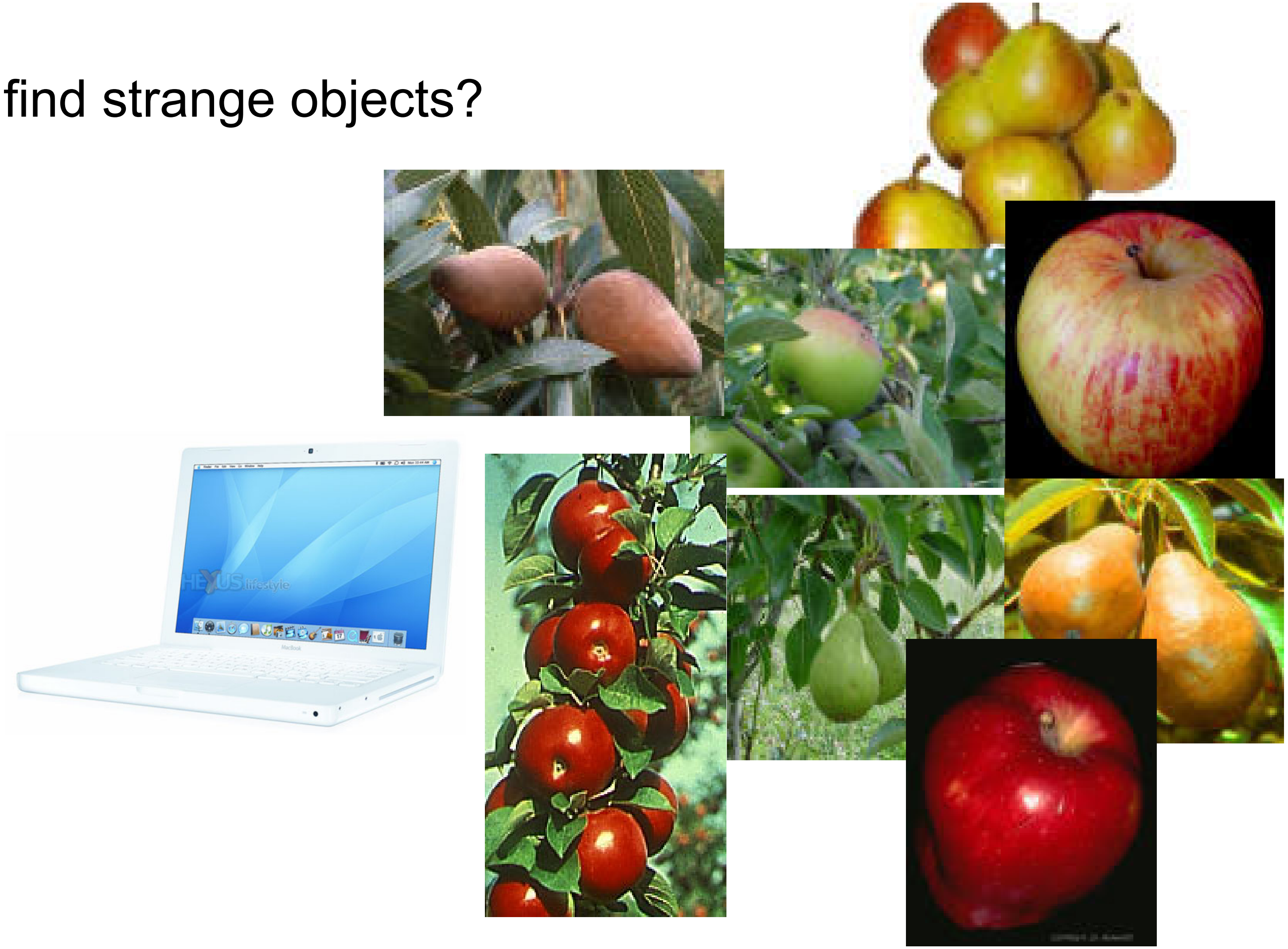
Clustering

- Can we find natural groups in the data?
- E.g. red vs green fruit



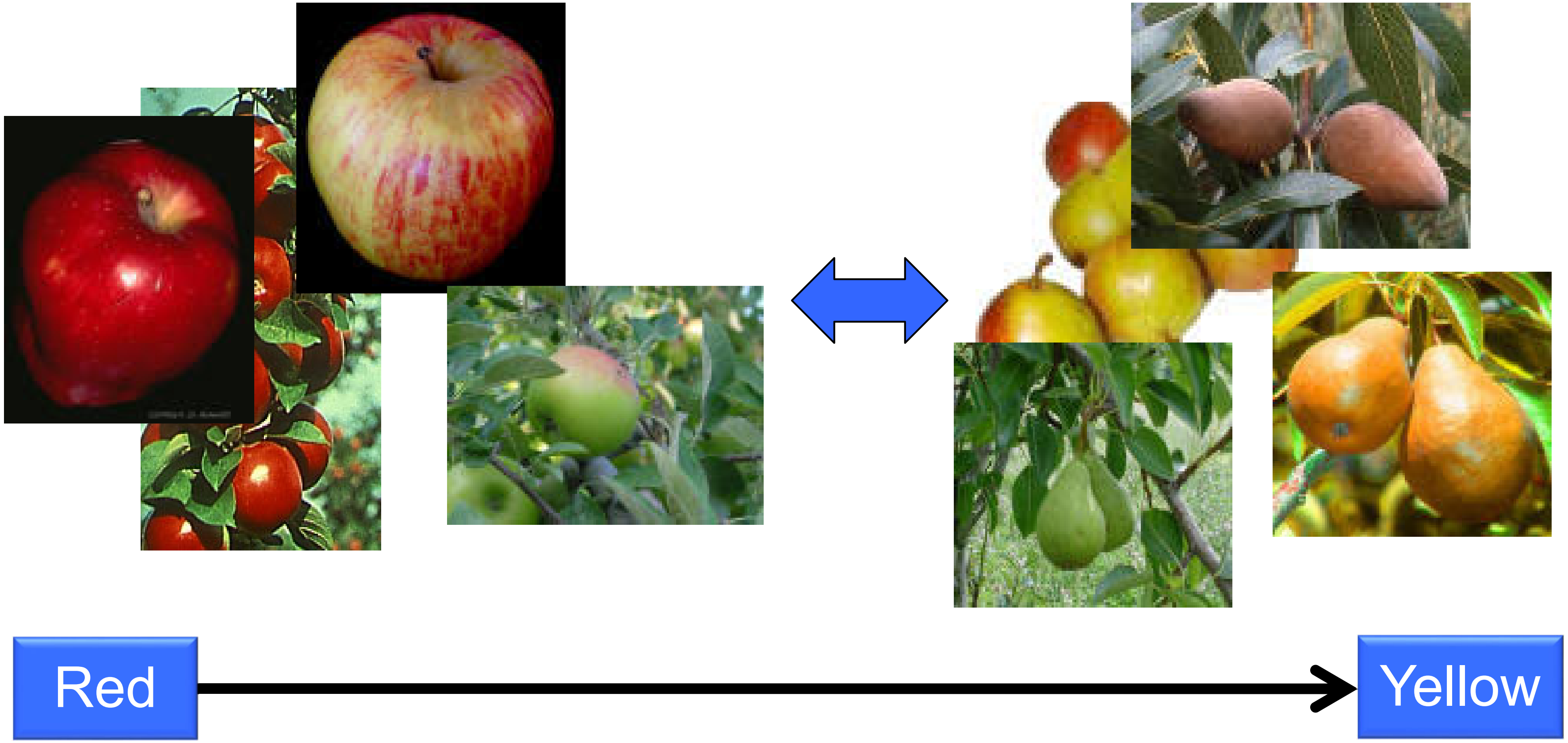
Outlier detection

- Can we find strange objects?



Dimensionality reduction

- Can we find predictive measurements?

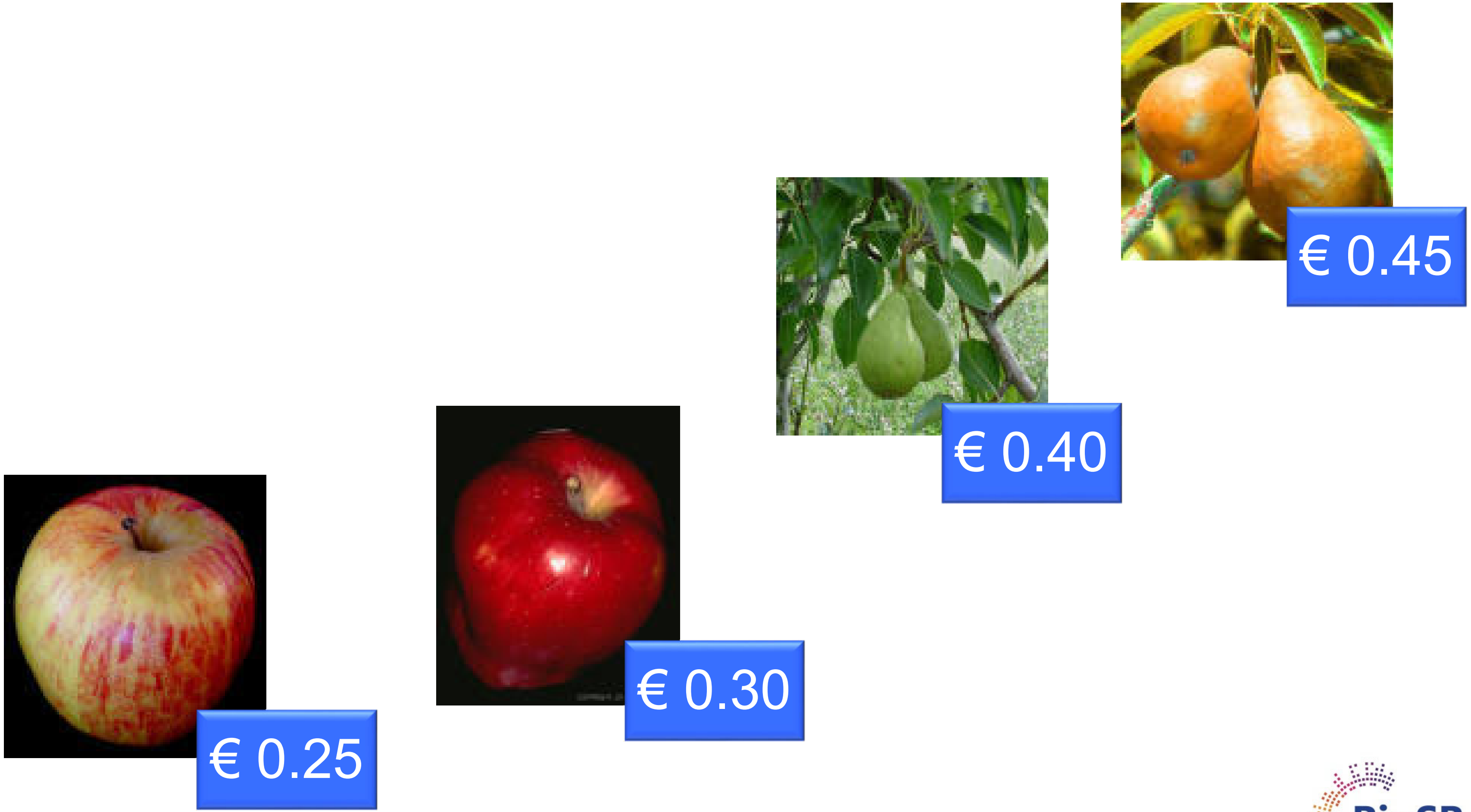


Red

Yellow

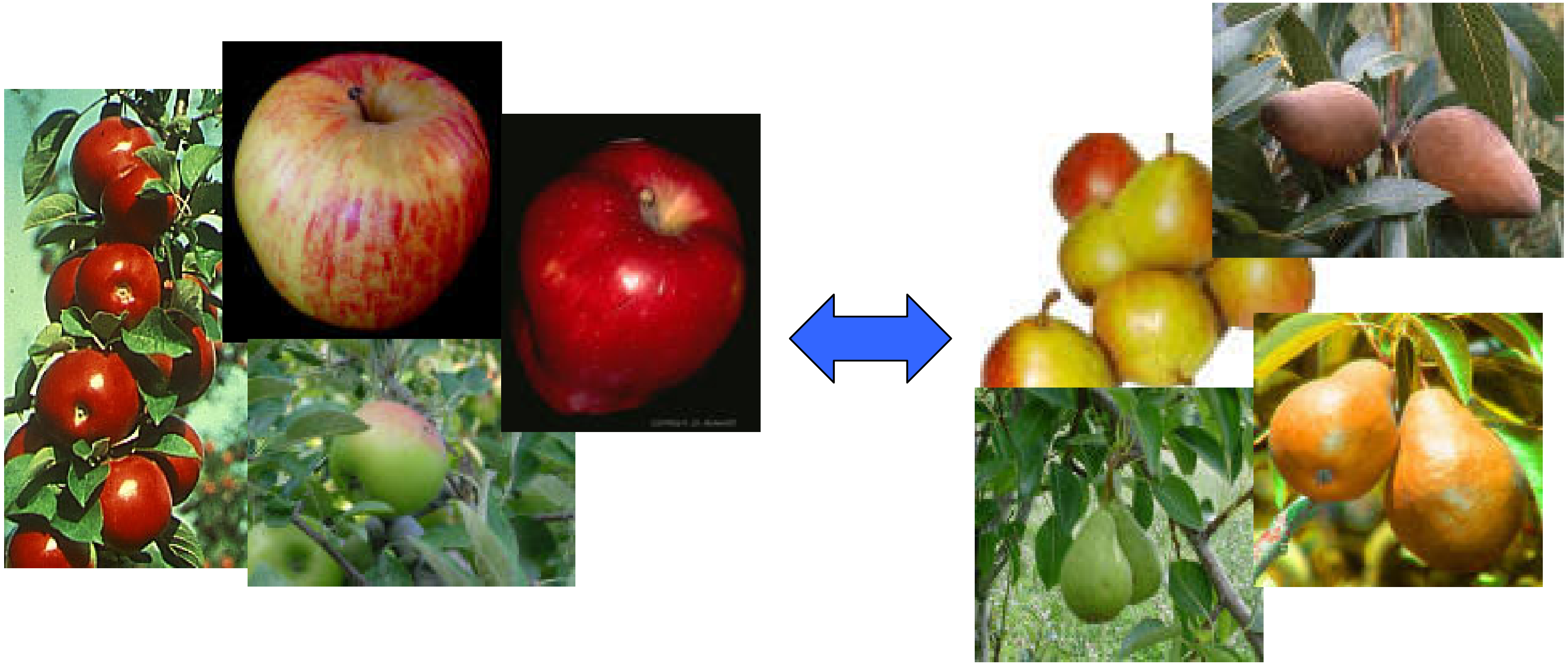
Regression

- Can we predict real-valued outputs?



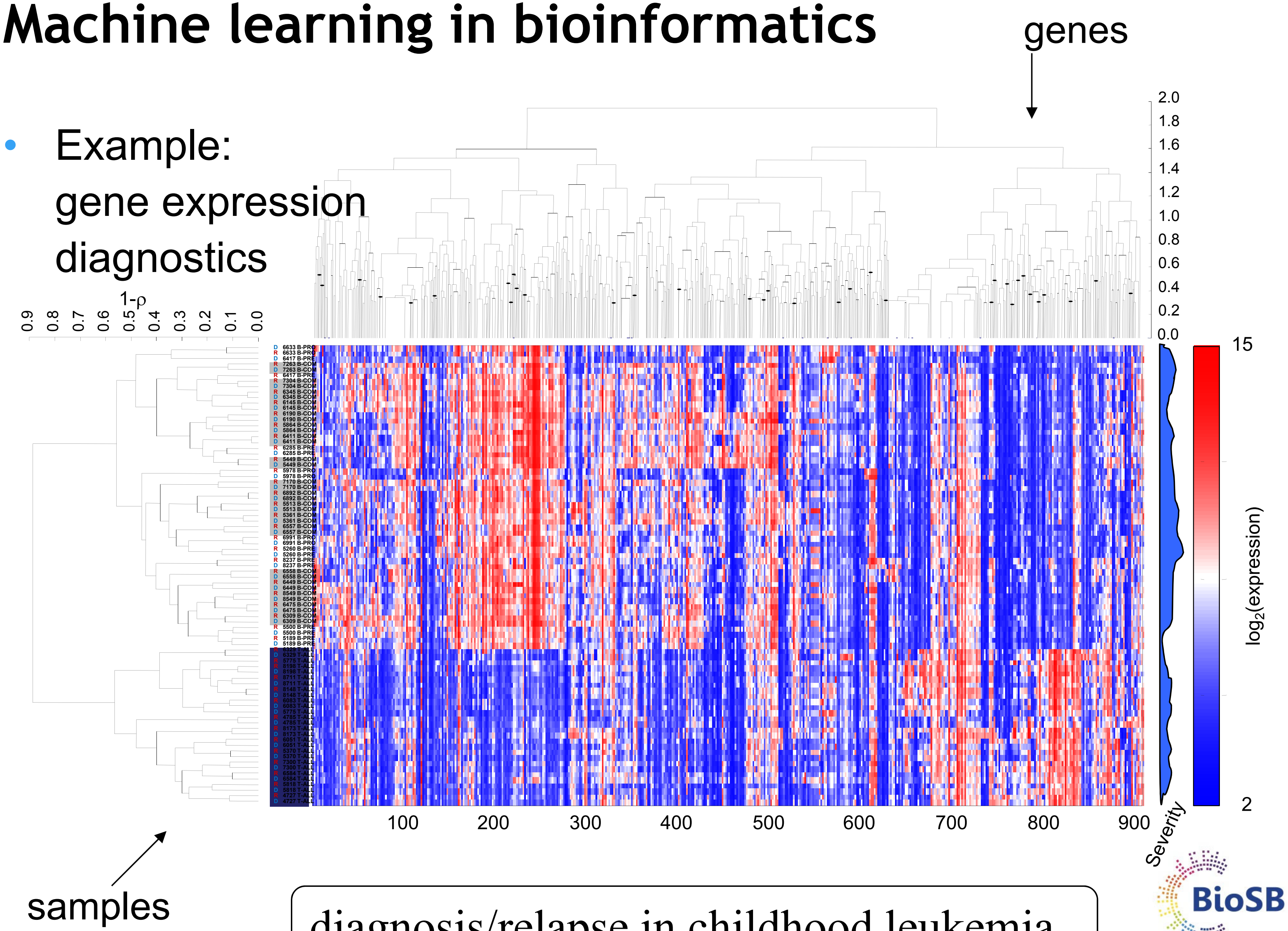
Classification

- Can we distinguish apples from pears?



Machine learning in bioinformatics

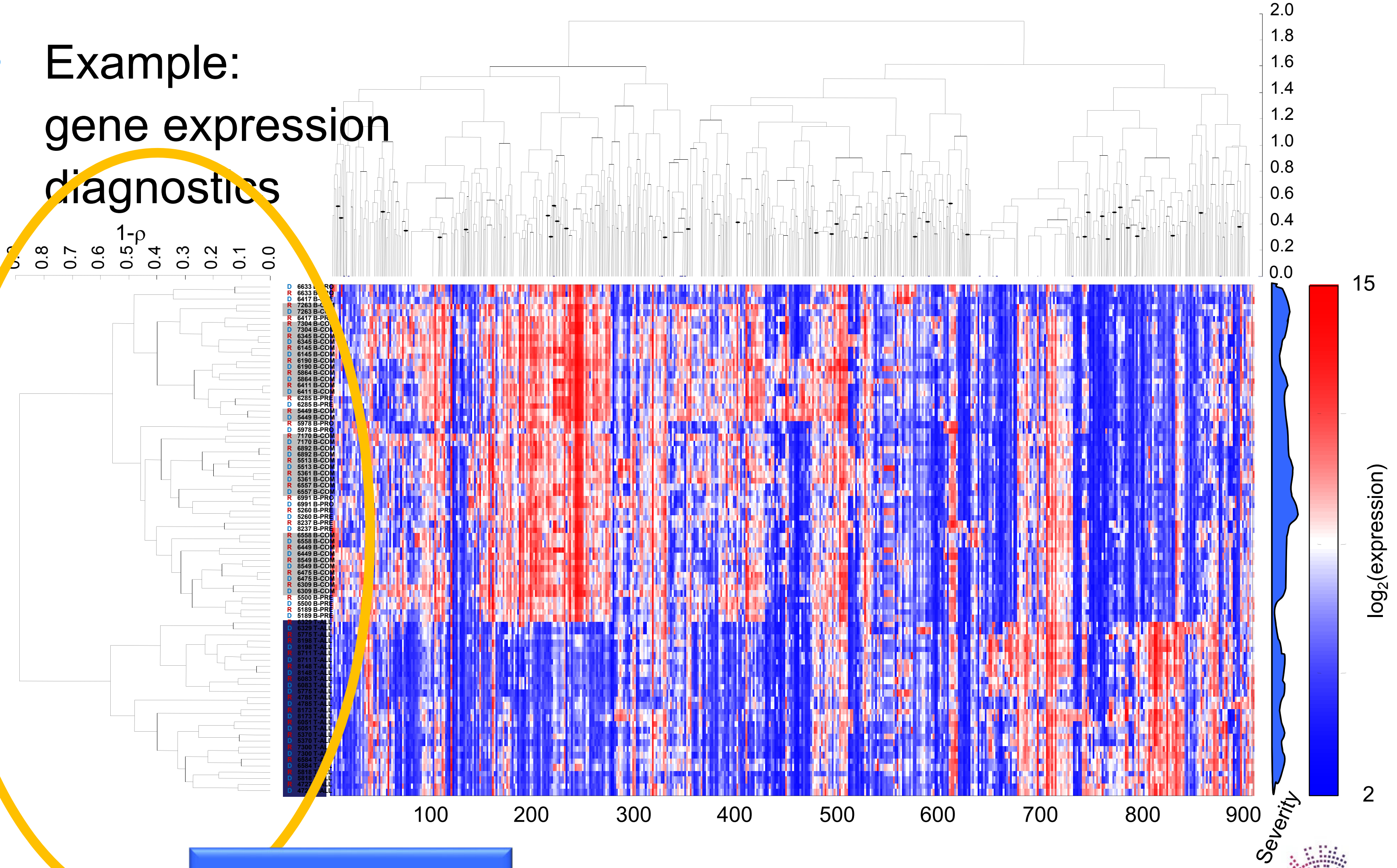
- Example:
  gene expression
  diagnostics



diagnosis/relapse in childhood leukemia

Machine learning in bioinformatics

- Example:
  gene expression diagnostics

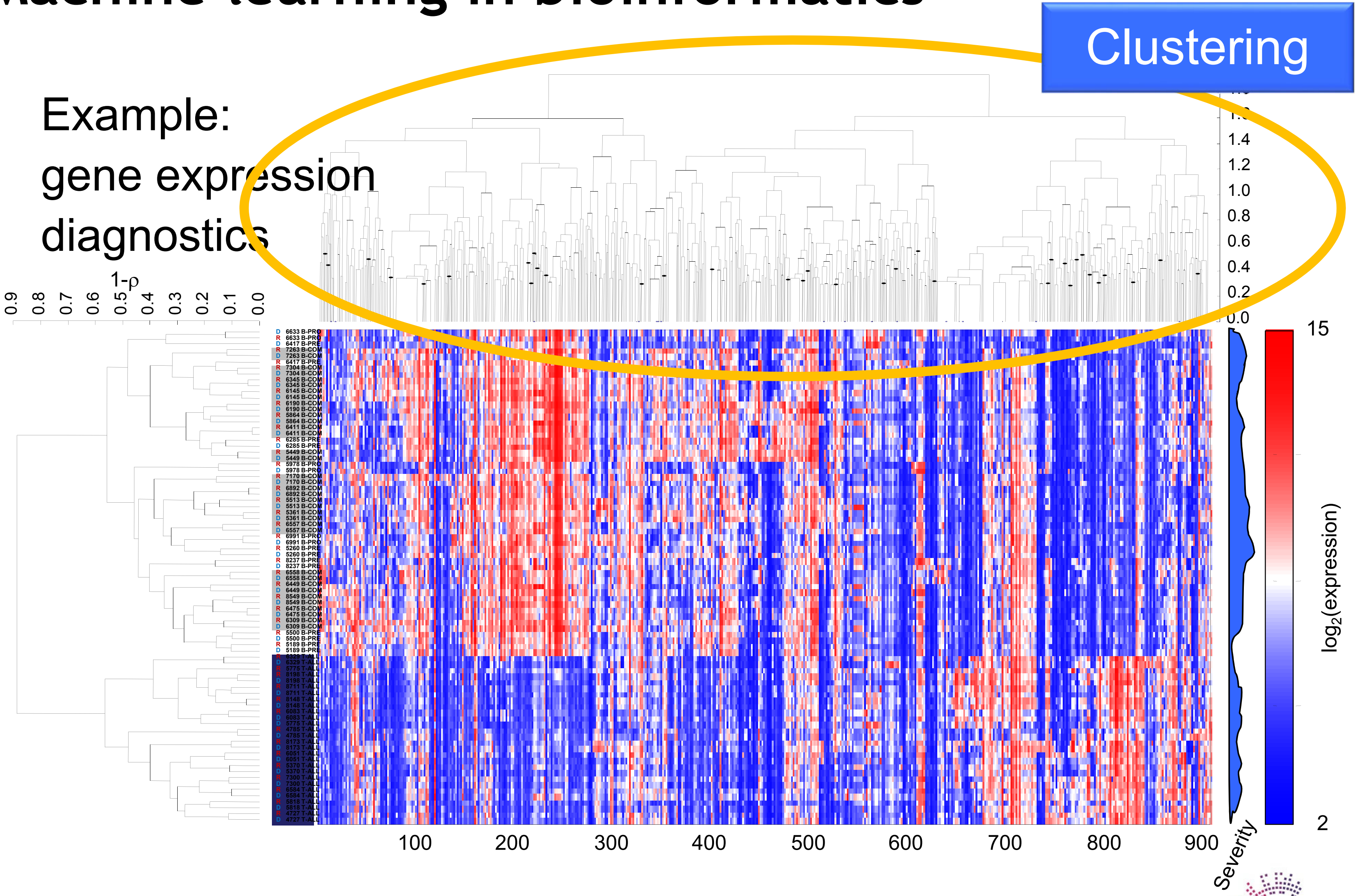


Clustering

Clustering of patients: similar subtypes of disease

Machine learning in bioinformatics

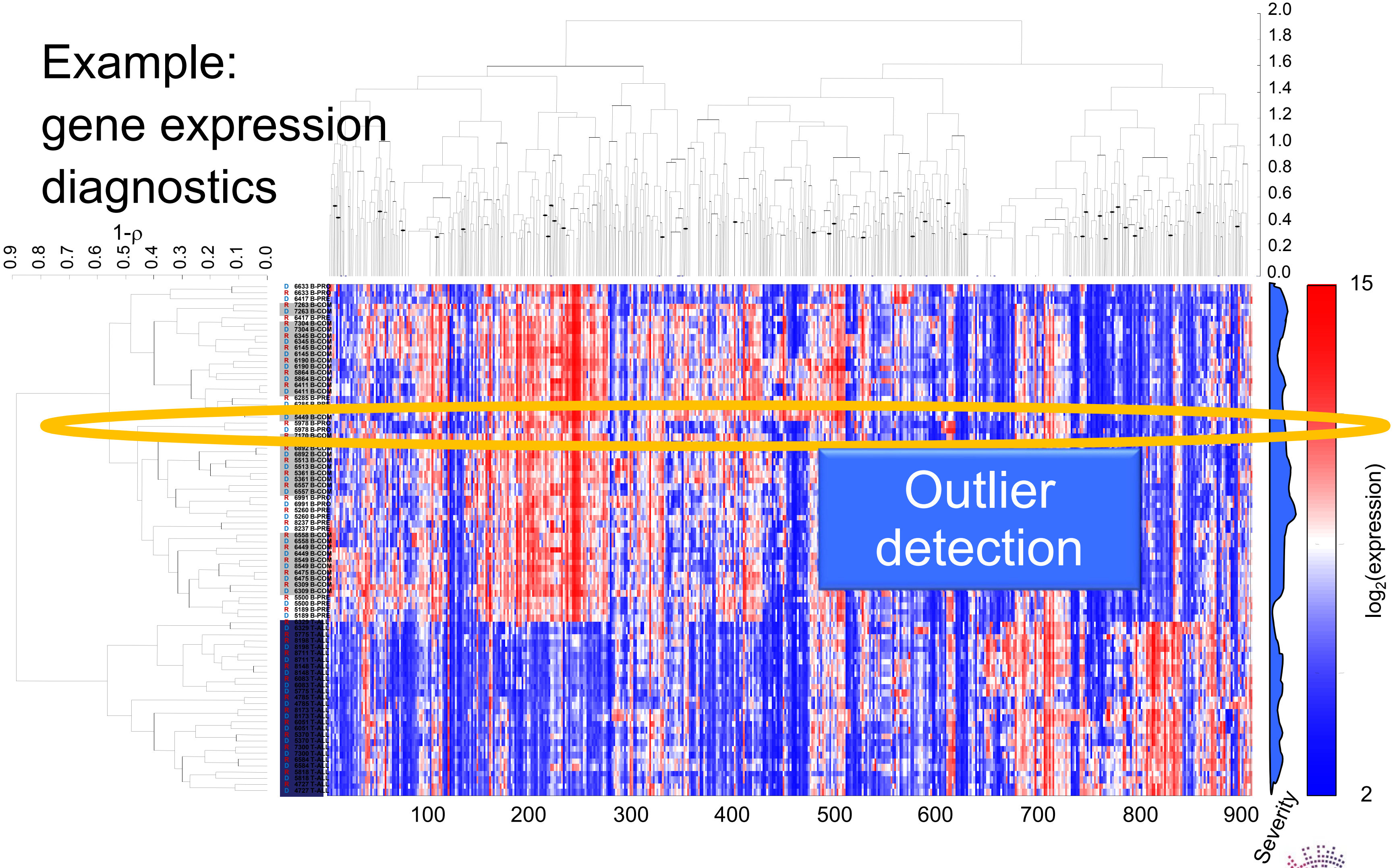
- Example:
  gene expression
  diagnostics



Clustering of genes: similar ‘disruptive’ processes

Machine learning in bioinformatics

- Example:
  gene expression
  diagnostics

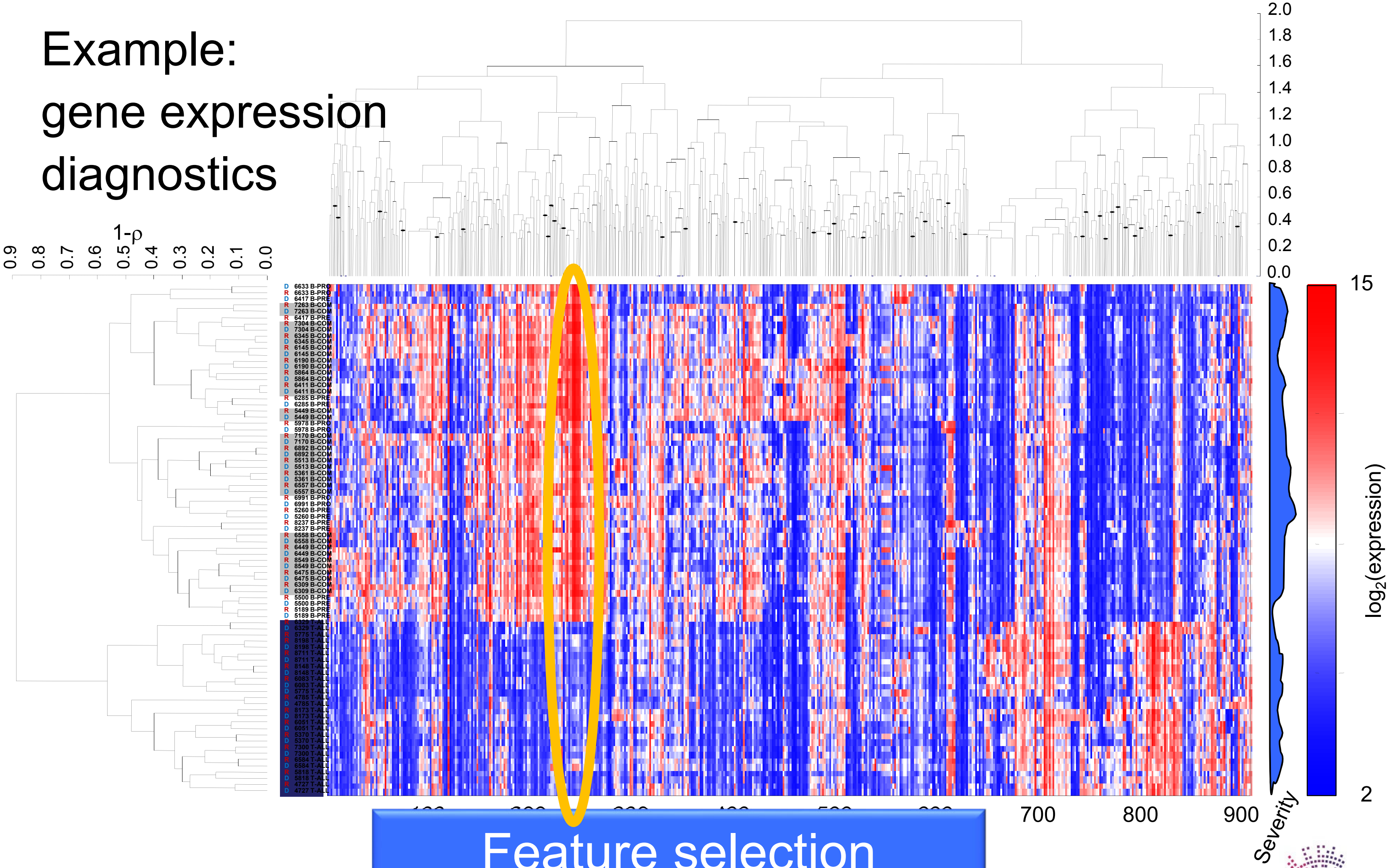


Outlier detection

Technical error / rare patient-rare genetic background

Machine learning in bioinformatics

- Example:
  gene expression
  diagnostics

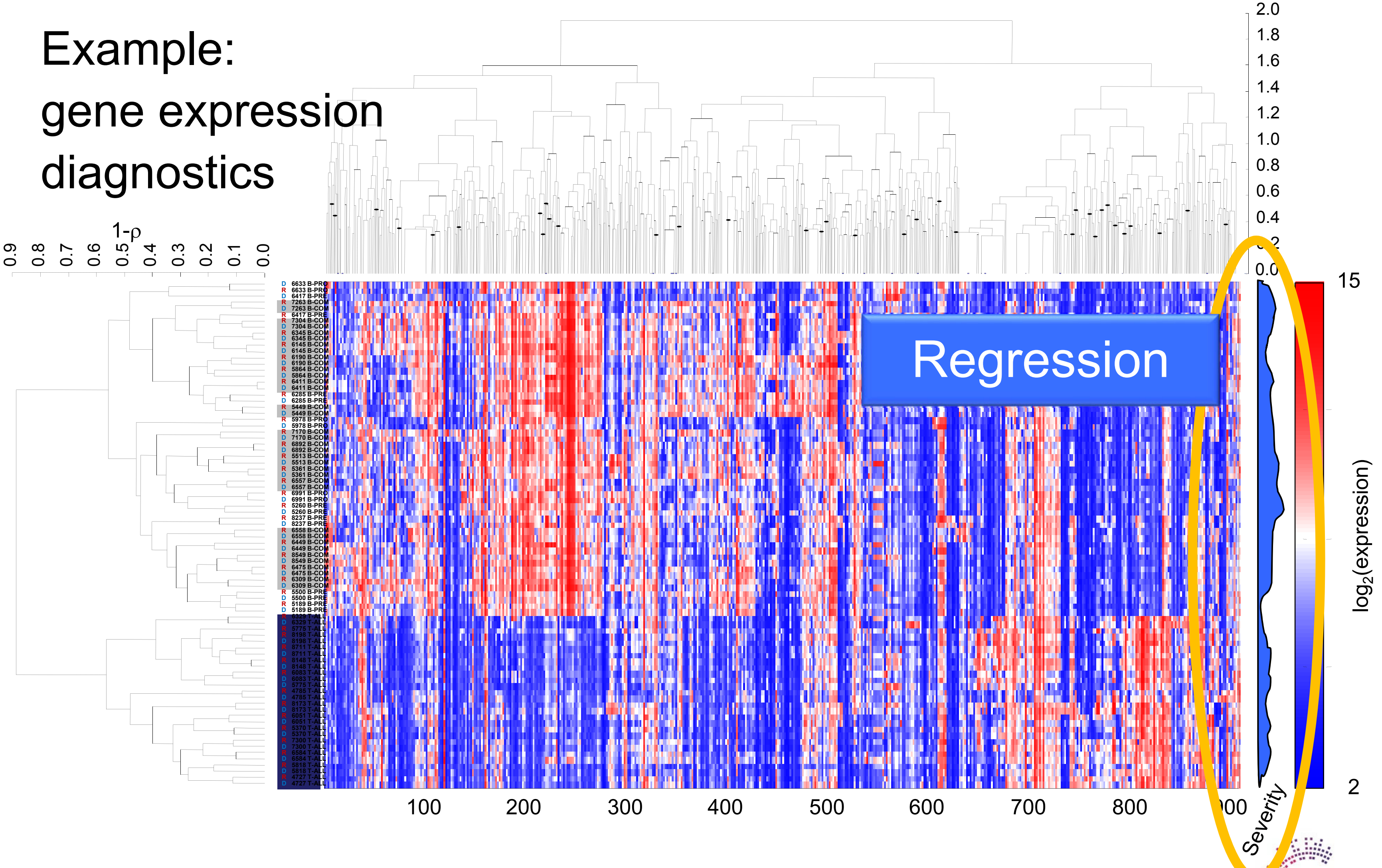


Feature selection
(dimensionality reduction)

Potential biomarkers

Machine learning in bioinformatics

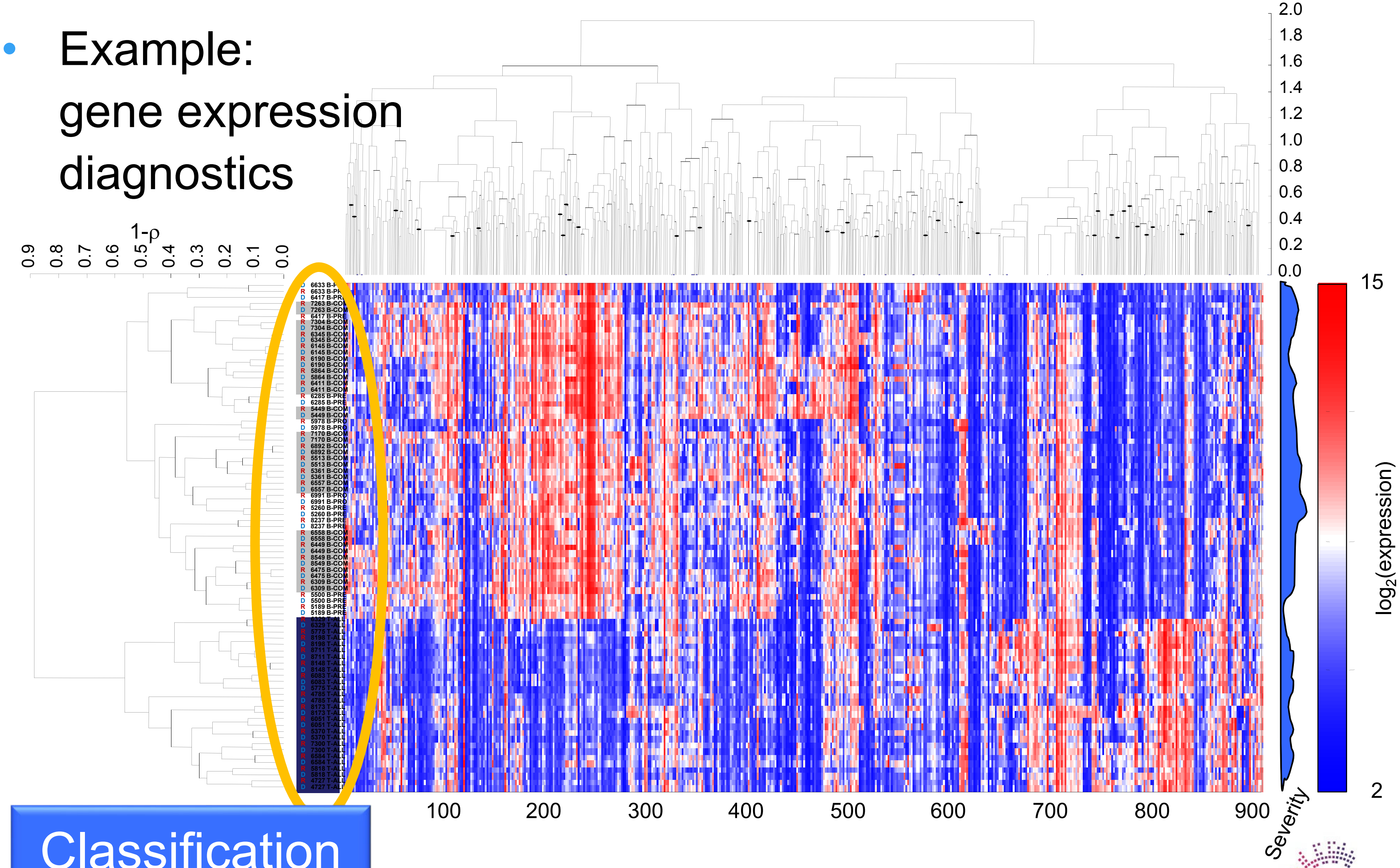
- Example:
  gene expression
  diagnostics



E.g. Predicting survival time

Machine learning in bioinformatics

- Example:
  gene expression
  diagnostics



Classification

E.g. Predicting metastasis

Machine learning in bioinformatics (2)

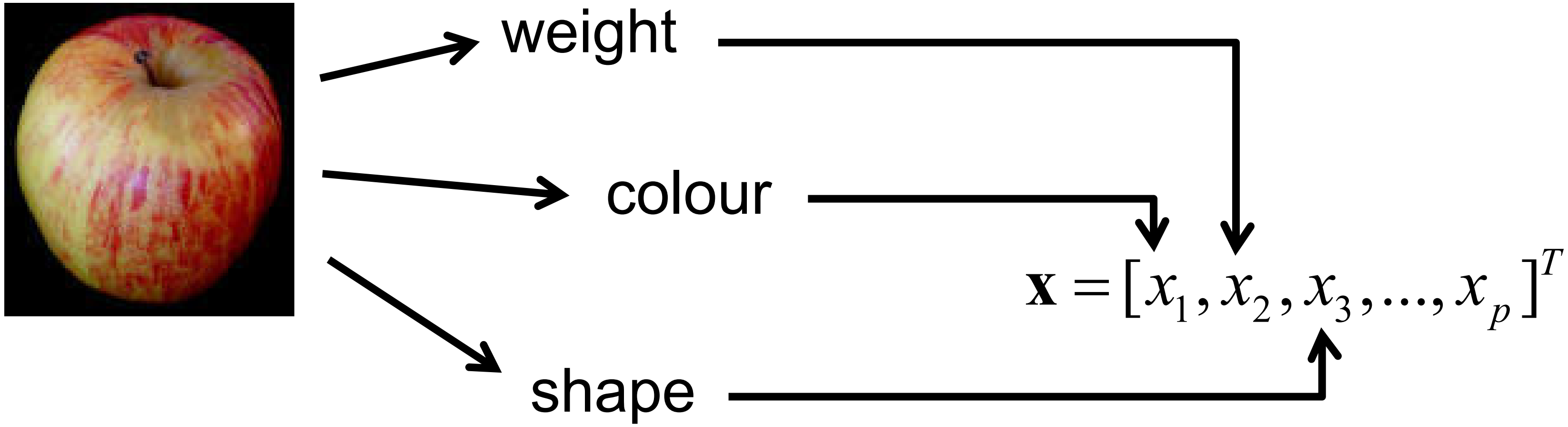
- Tools applicable to any type of biological data

- Examples:
  - Protein sequence data:
    - Clustering: finding orthologous groups
    - Classification: prediction of EC number, subcellular localization, …
    - Regression: predicting secondary structure
  - TF binding data (ChIP):
    - Clustering: finding functional gene groups
    - Classification: predicting gene annotation
    - Regression: finding cis-regulatory modules
  - …

Terminology

Measurements and features

- To automate these tasks, we have to find a mathematical *representation* of objects
- Objects are usually represented by *features*, i.e. sets of useful *measurements* obtained from some *sensors*



weight

colour

shape

$$\mathbf{x} = [x_1, x_2, x_3, \ldots, x_p]^T$$

Measurements and features (2)

- This course assumes measurements as given, i.e. sensor accuracy etc. are not *explicitly* modeled

- However,
  - in general measurements will never be perfect
  - objects within a class will vary intrinsically

- Hence, we need statistics to model all variation

This is important!
If we know everything and there is no noise, you'll need different algorithms/models

Datasets

- A *dataset* is a set of measurements on many objects
- For clustering:

Object	Weight	Colour
Apple #1	25	36
Apple #2	20	34
Apple #3	35	40
Pear #1	35	55
Pear #2	37	55
Pear #3	40	57
Pear #4	36	41

Datasets

- A *dataset* is a set of measurements on many objects
- For regression:

Object	**Weight**	**Colour**	**Price**
Apple #1	25	36	0.21
Apple #2	20	34	0.17
Apple #3	35	40	0.33
Pear #1	35	55	0.41
Pear #2	37	55	0.26
Pear #3	40	57	0.35
Pear #4	36	41	0.29

Datasets

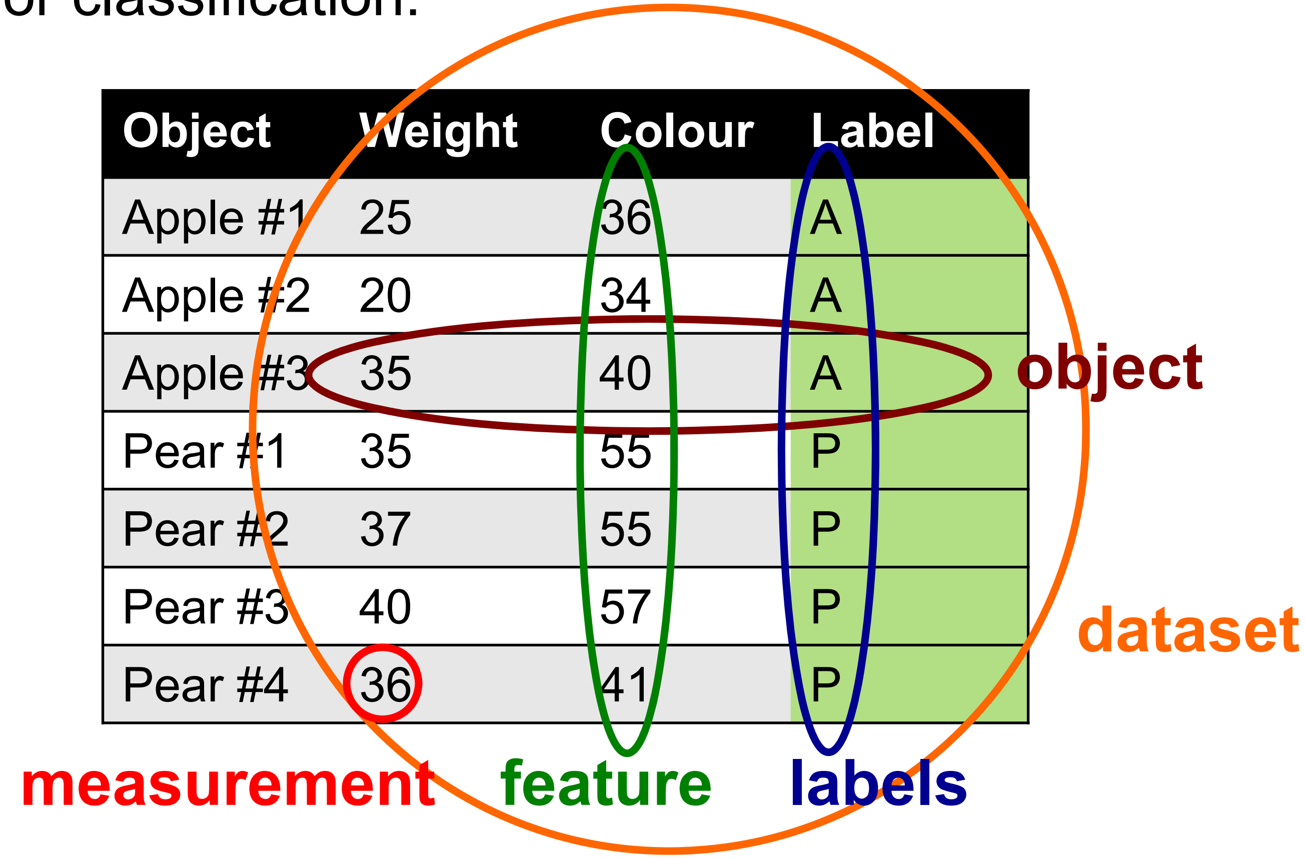
- A *dataset* is a set of measurements on many objects
- For classification:

Object	Weight	Colour	Label
Apple #1	25	36	A
Apple #2	20	34	A
Apple #3	35	40	A
Pear #1	35	55	P
Pear #2	37	55	P
Pear #3	40	57	P
Pear #4	36	41	P

Datasets

- A *dataset* is a set of measurements on many objects

- For classification:



Object	Weight	Colour	Label
Apple #1	25	36	A
Apple #2	20	34	A
Apple #3	35	40	A
Pear #1	35	55	P
Pear #2	37	55	P
Pear #3	40	57	P
Pear #4	36	41	P

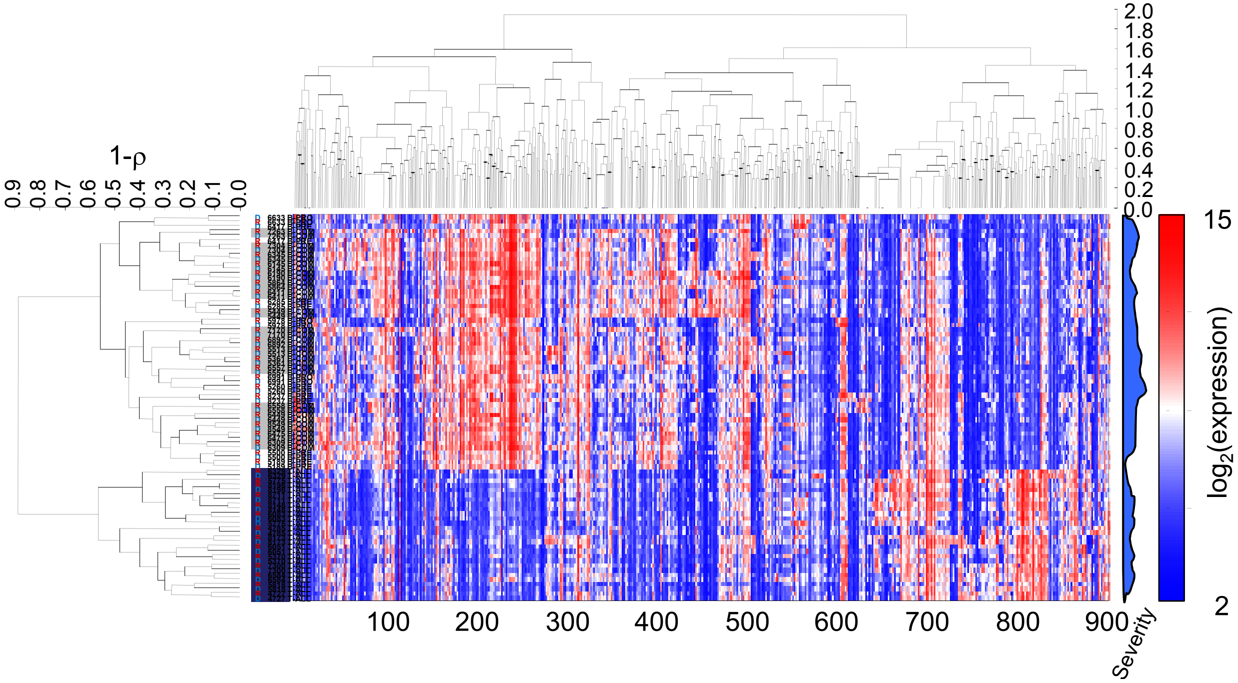
object

dataset

measurement **feature** **labels**

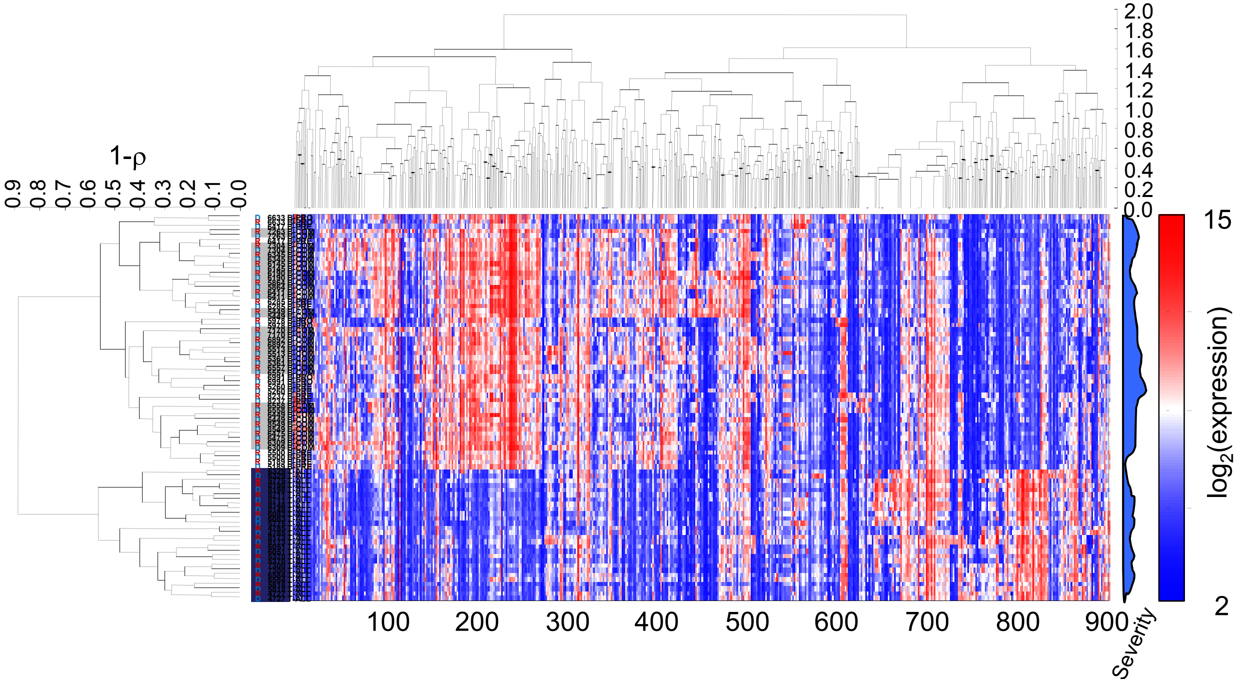
Datasets (2)

- What objects, labels/targets and features are depends on the problem...
- Gene expression-based diagnostics:
  - object: patient
  - feature: gene expression, copy number, mutational pattern, ….
  - label: relapse; regressor/dependent variable: survival time



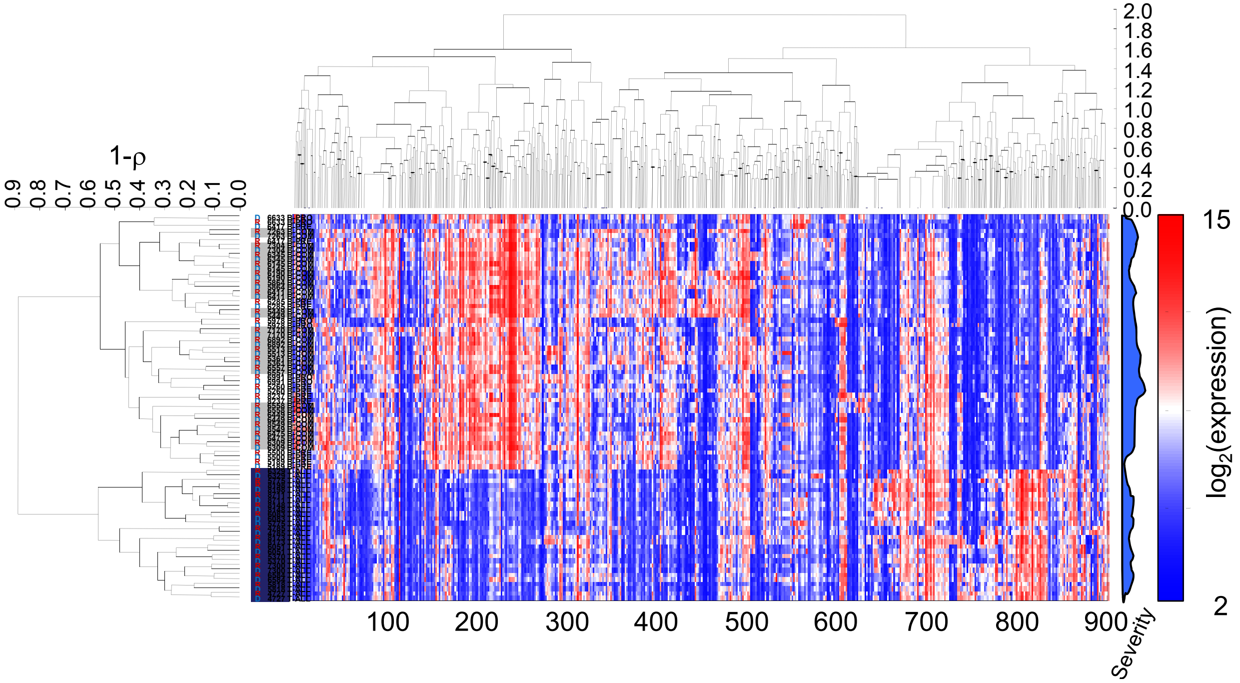
Datasets (2)

- What objects, labels/targets and features are depends on the problem...
- Protein-protein interactions:
  - object: protein PAIR
  - feature: gene expression correlation, difference in annotation, …
  - label: complex or not; regressor/dependent variable: binding strength



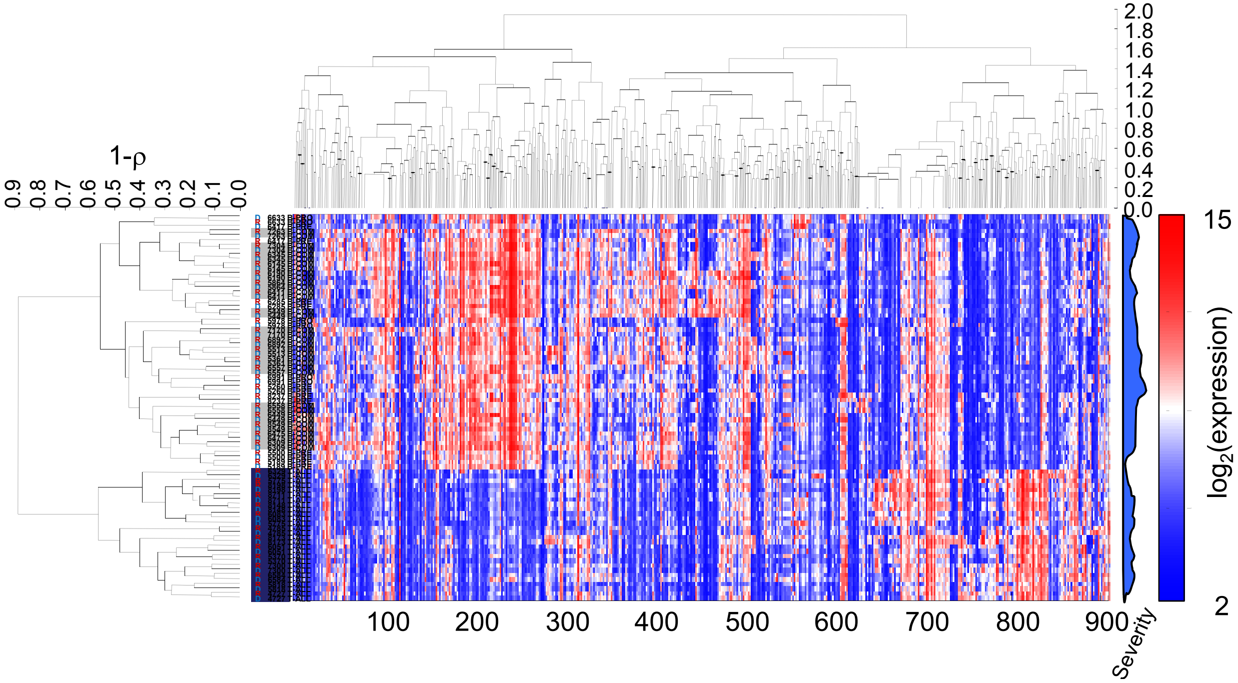
Datasets (2)

- What objects, labels/targets and features are depends on the problem...
- Gene prediction:
  - object: gene
  - feature: sequence (representation), conservation of sequence, …
  - label: gene or not; regressor/dependent variable: conservation



Datasets (2)

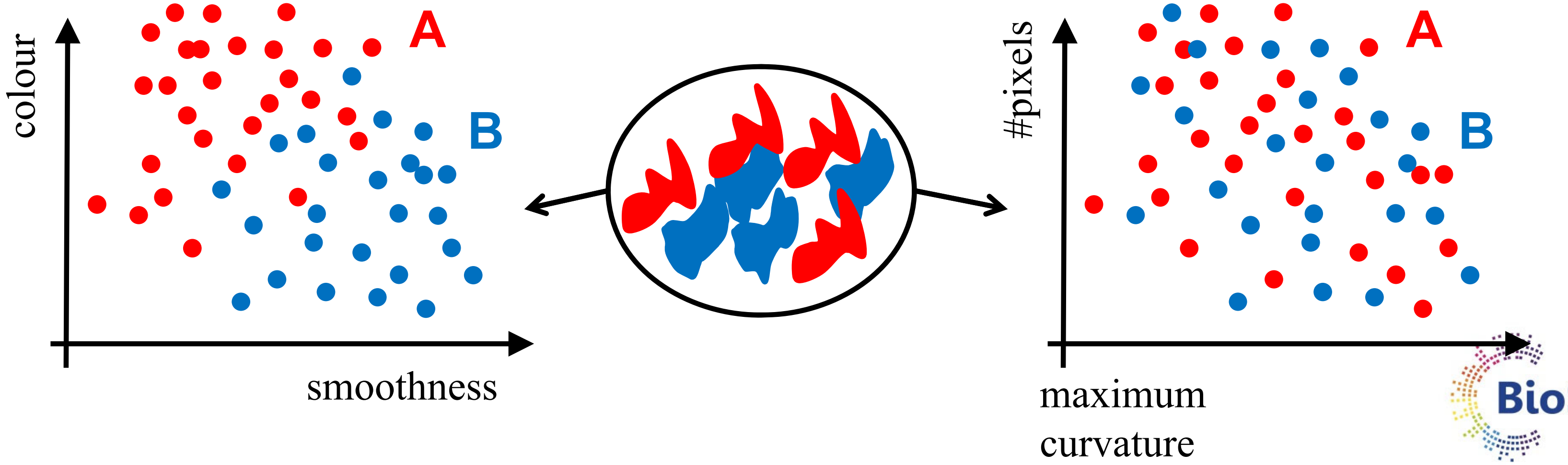
- What objects, labels/targets and features are depends on the problem…
- TFBS detection:
  - object: location on genome
  - feature: ChIP-seq, sequence features, distance to TSS …
  - label: TFBS or not; regressor/dependent variable: specificity



Measurements and features (3)

- Problems
  - simple
  - knowledge present
  - a few good features
  - almost separable classes (classification) or a linear relation (regression)

  - complex
  - lack of knowledge
  - many poor features
  - overlapping classes (classification) or highly non-linear relation (regression)

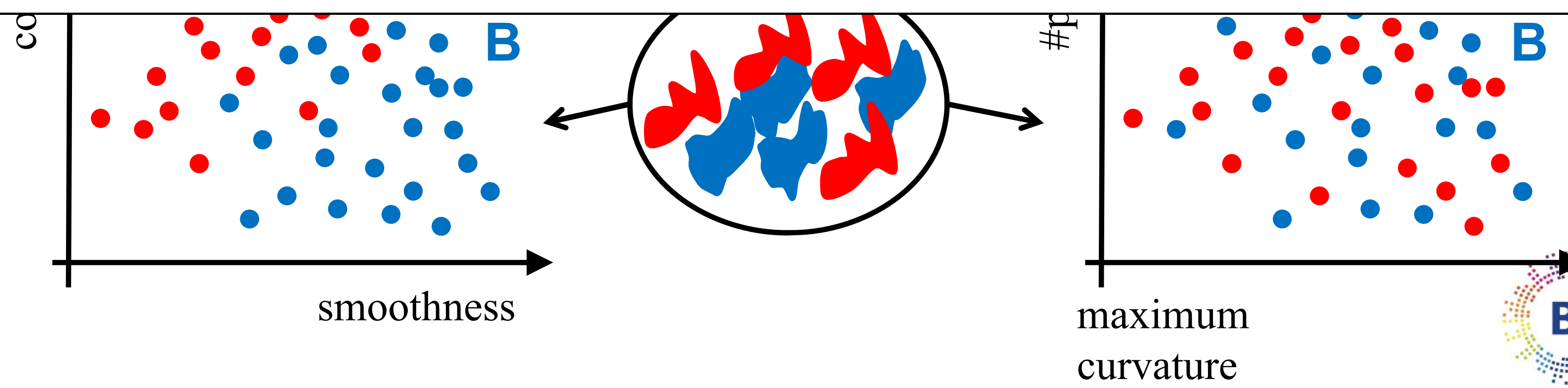


Measurements and features (3)

- Problems
  - simple
  - knowledge present
  - a few good features
  - complex
  - lack of knowledge
  - many poor features
  - overlapping classes

Features (object representations) are important!

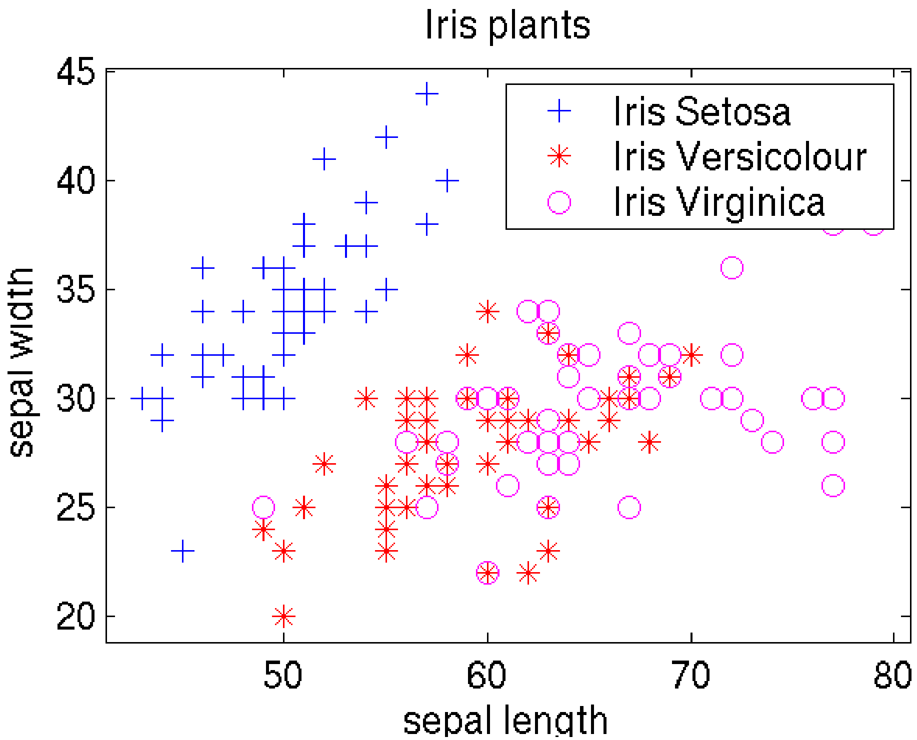
We don’t deal too much with which features are measured, although we will touch upon derived features (Day 5: kernels) and learning features (Day 5: neural networks)



Feature space

- We can interpret objects as vectors in a vector space

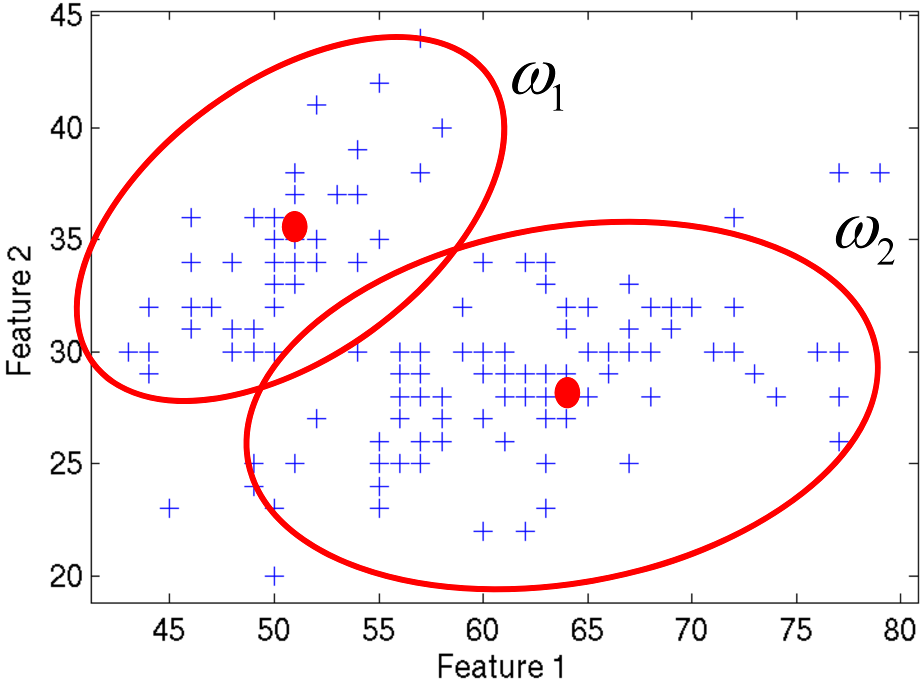
$$\mathbf{x} = [x_1, x_2, x_3, \ldots, x_p]^T$$



Iris flower dataset, introduced by **Ronald Fisher (famous statistician)** in 1936 as an example of discriminant analysis

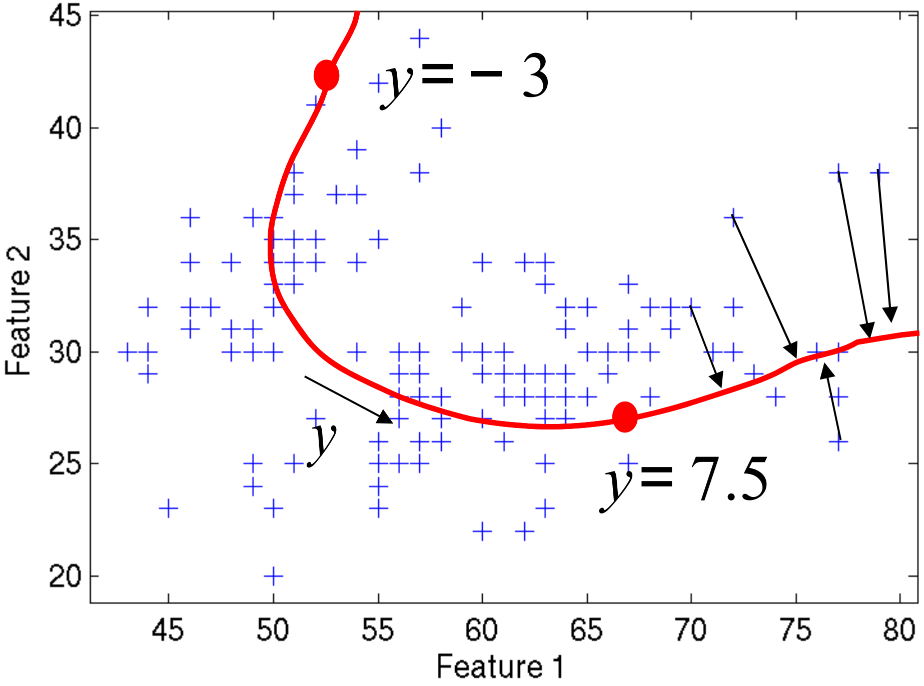
Clustering

- Given unlabeled data $\boldsymbol{x}$,
  find labels ω for natural groups in the data



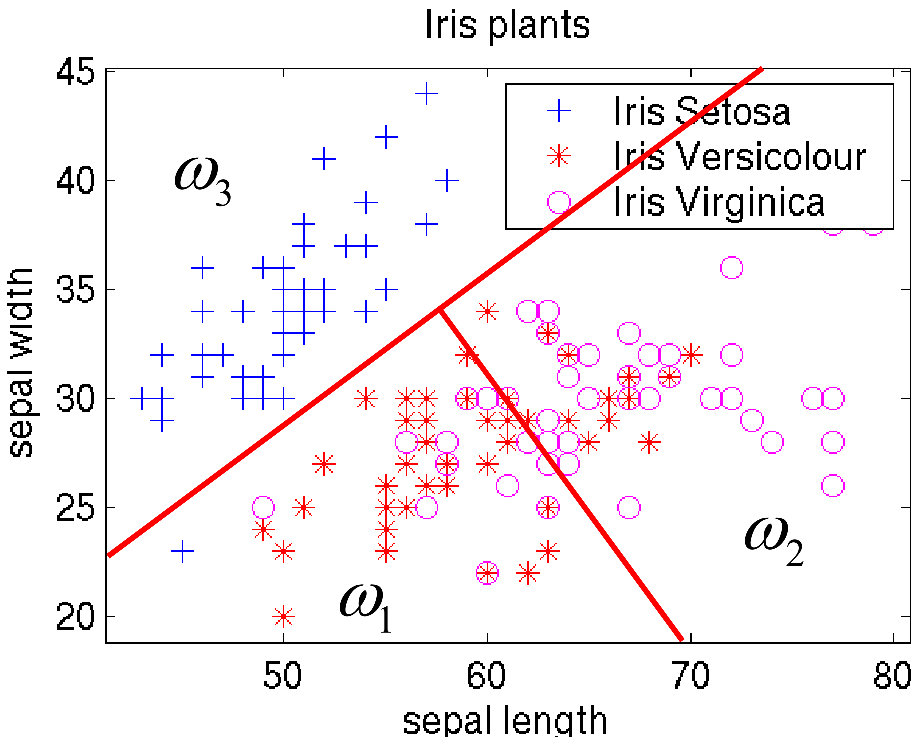
Dimensionality reduction

- Given unlabeled data x,
  map it to a lower dimensional feature vector y



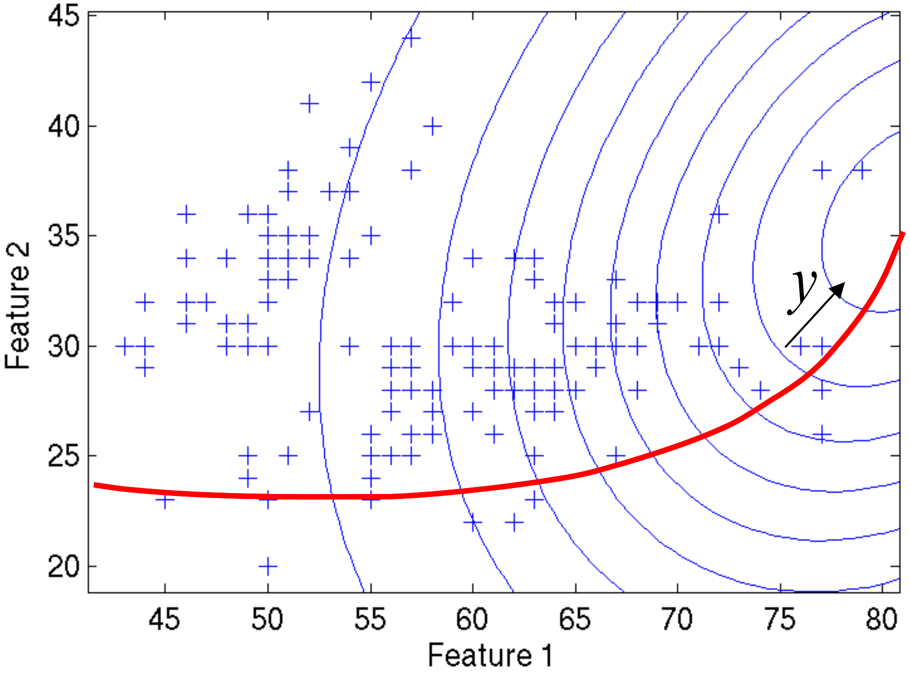
Classification

- Given labeled data $\boldsymbol{x}$,
  assign each point in feature space to a class ω_i
  (in effect partitioning the feature space)



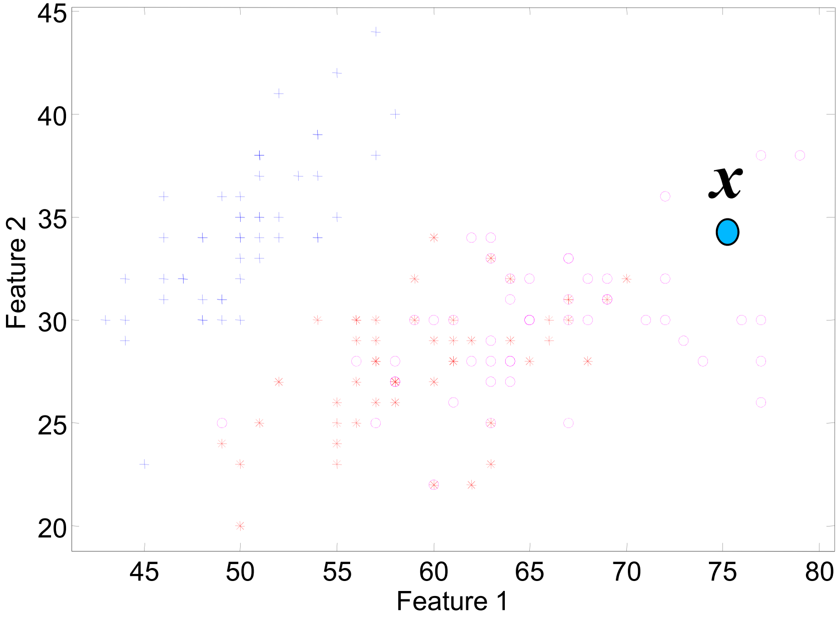
Regression

- Given labeled data $\boldsymbol{x}$,
  assign each point in feature space a real-valued output y



General model

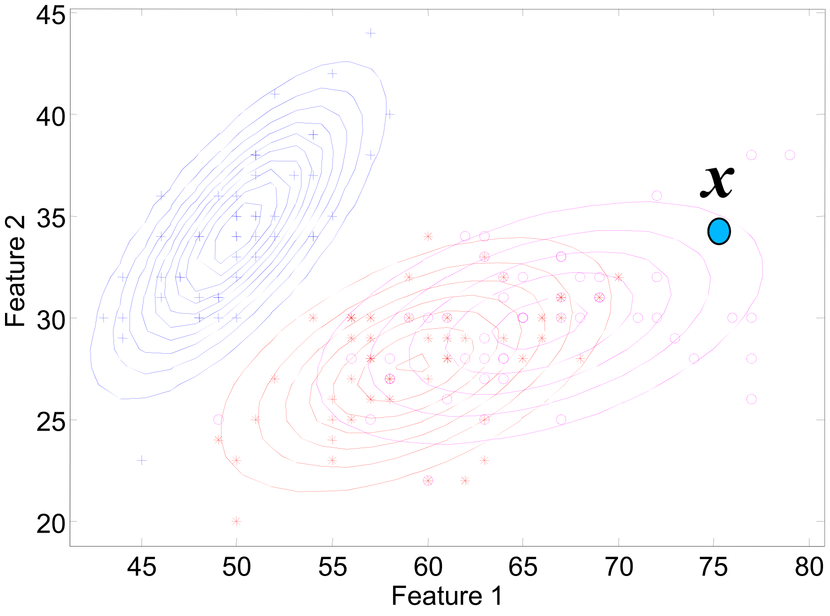
- Construct a model $f(\boldsymbol{x})$ that outputs ω or y
- This model should be fit to the data



$$f(\boldsymbol{x}) = \omega \text{ or } f(\boldsymbol{x}) = y$$

General model (2)

- Construct a model $f(\boldsymbol{x})$ that outputs ω or y
- This model should be fit to the data
- Ideally, we know $p(y \mid \boldsymbol{x})$ or $p(\omega \mid \boldsymbol{x})$ over the entire feature space



$p(y \mid \boldsymbol{x})$

or

$p(\omega \mid \boldsymbol{x})$

$$\Longrightarrow \quad f(\boldsymbol{x}) = \omega \text{ or } f(\boldsymbol{x}) = y$$

if we know the probability distributions, we can make the most informed decision

General model (3)

- Construct a model $f(\boldsymbol{x})$ that outputs ω or y
- This model should be fit to the data
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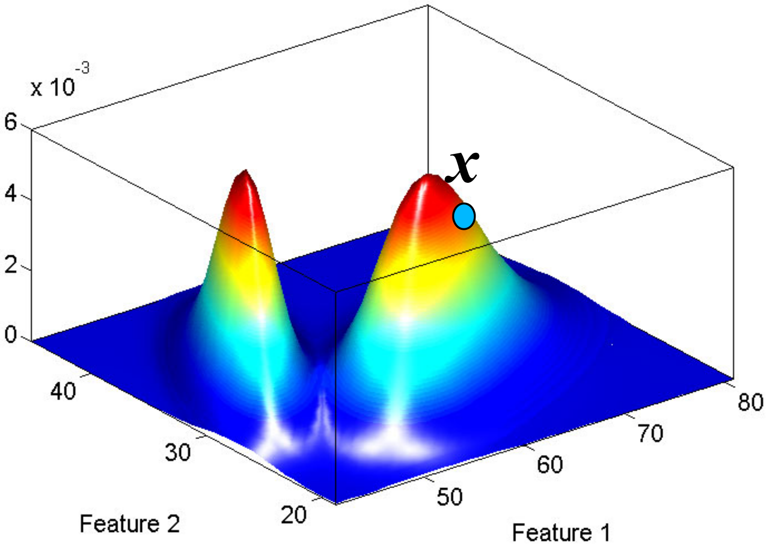


$$p(y \mid \boldsymbol{x})$$

or

$$p(\omega \mid \boldsymbol{x})$$

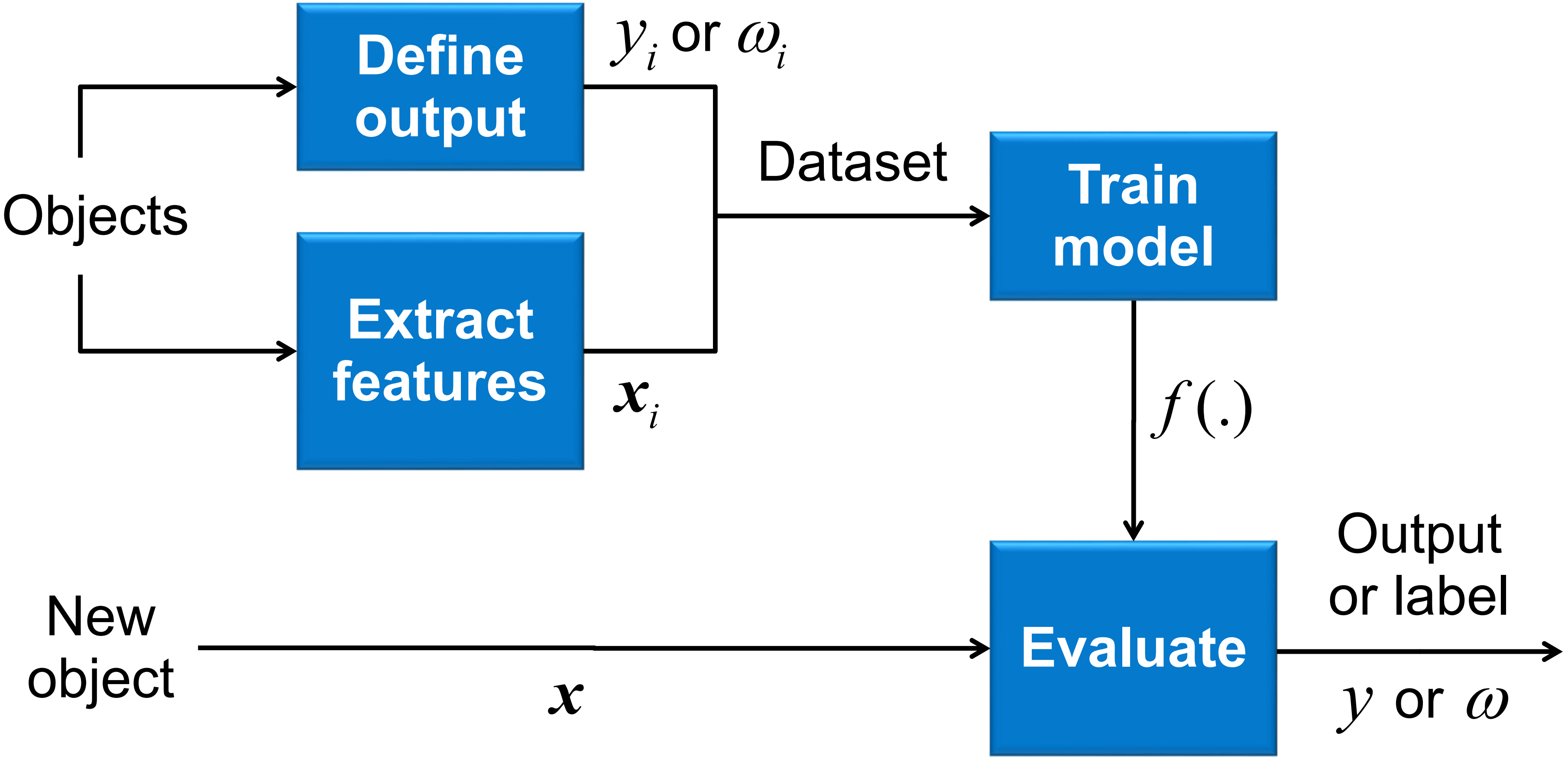
$$\Longrightarrow \quad f(\boldsymbol{x}) = \omega \text{ or } f(\boldsymbol{x}) = y$$

if we know the probability distributions, we can make the most informed decision

General model (4)

- Clustering: find cluster labels ω given object $\boldsymbol{x}$
  fit model using dataset $\{\boldsymbol{x}_i\}$ $\quad p(\omega \mid \boldsymbol{x})$
- Dimensionality reduction: find mapping y given object $\boldsymbol{x}$
  fit model using dataset $\{\boldsymbol{x}_i\}$ $\quad p(y \mid \boldsymbol{x})$
- Classification: find class labels ω given object $\boldsymbol{x}$
  fit model using dataset $\{\boldsymbol{x}_i, \omega_i\}$ $\quad p(\omega \mid \boldsymbol{x})$
- Regression: find target y given object $\boldsymbol{x}$
  fit model using dataset $\{\boldsymbol{x}_i, y_i\}$ $\quad p(y \mid \boldsymbol{x})$

Machine learning pipeline



Objects

Define output

Extract features

y_i or ω_i

$\boldsymbol{x}_i$

Dataset

Train model

$f(.)$

New object

$\boldsymbol{x}$

Evaluate

Output or label

y or ω

10min break

Statistics

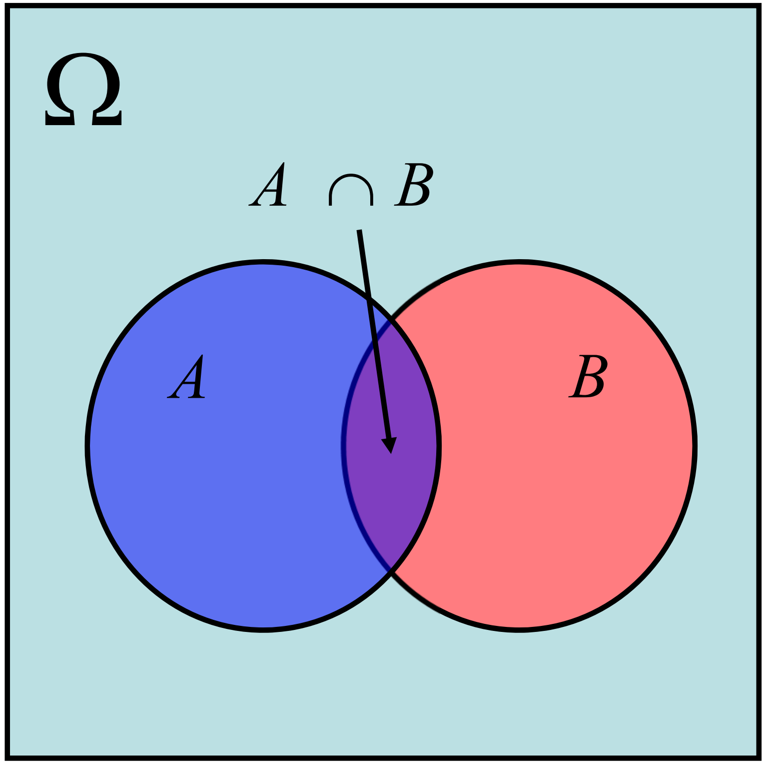
Required background

- The course is aimed at PhD students with a background in bioinformatics, systems biology, computer science or a related field, and life sciences. A working knowledge of basic statistics and linear algebra is assumed.

- Self-assessment; if you have problems, read the primers
- Now, a brief recap

Recall: probability

- Ω : all possible outcomes (sample space)
  e.g. the number of eyes on a dice: 1, 2, 3, 4, 5, 6
- $A \in \Omega$: event
  e.g. "throwing a 3"
- P : probability measure
  - $0 \leq P(A) \leq 1$
  - $P(\Omega) = 1$
  - $P(A \cup B) =$
    $P(A) + P(B) - P(A \cap B)$
  - E.g. $P(A) = 1/6$



Recall: probability (3)

- Subjective approach:
  “the probability of A is a number between 0 and 1
  indicating how likely people believe A to be true”

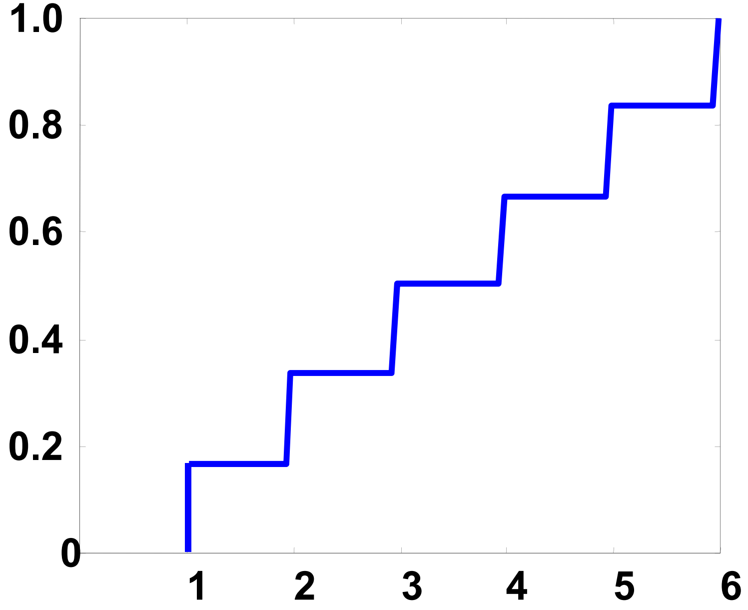
- Frequentist approach:
  “the probability of A is a number between 0 and 1
  indicating the average ratio of A being true in
  a large number of repeated experiments”

- Is really a philosophical debate...
  the “right” approach depends on the problem
  and the data available

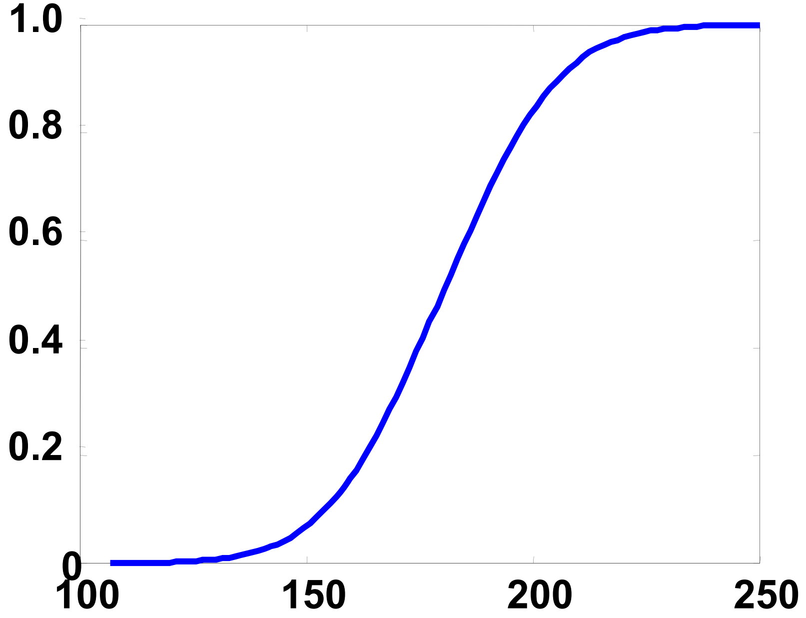
problems (can) arise in interpretation: what does it mean?

Recall: CDFs

- Cumulative distribution function
- $P_X(x) = F(x)$: probability that $X \leq x$, $\Re \rightarrow [0,1]$



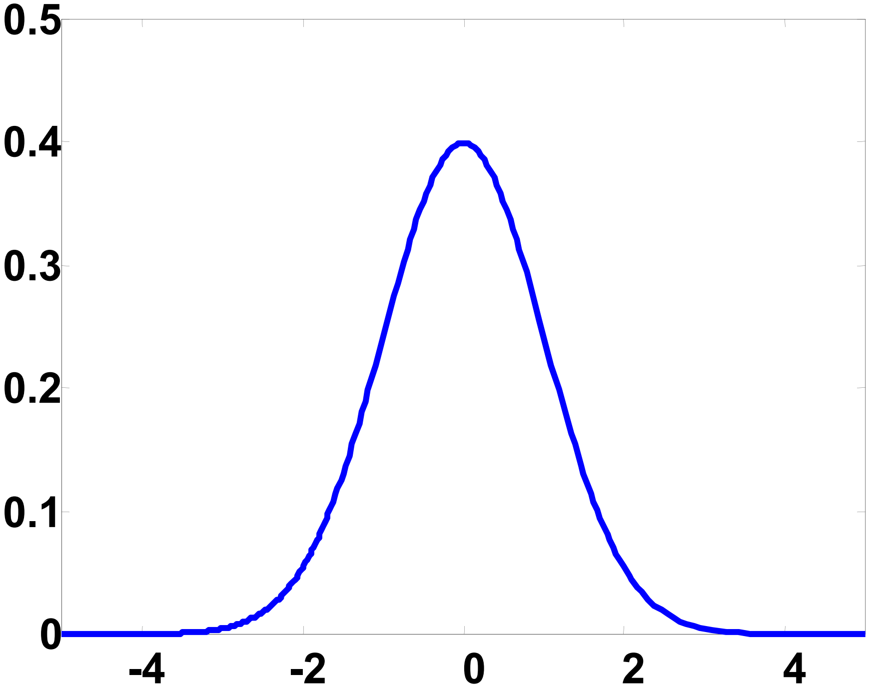
e.g. 10,000 dice throws



10,000 body lengths

Recall: PDFs

- $p(x) = \dfrac{dP(x)}{dx}$: probability density function
  - $p(x) \geq 0$
  - $\int_{-\infty}^{\infty} p(x)dx = 1$
  - $\int_{a}^{b} p(x)dx = P(a \leq x \leq b)$



- **$p(x)$ is not the probability of X being x !**

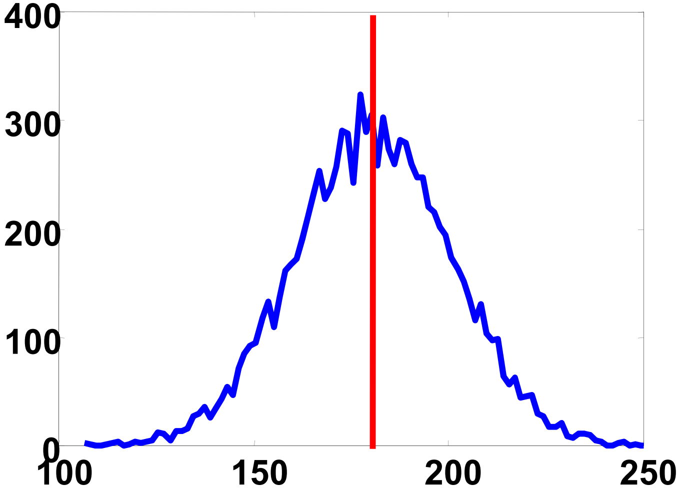
Recall: expectation

- Expectation: mean of distribution,

$$\mu = \mathrm{E}[X] = \int_{-\infty}^{\infty} x \;\; p(x) \;\; dx$$

- Note: expectations are over entire distributions; on data sets $\{x\}$ we can only estimate the mean,

$$m = \hat{\mu} = \frac{1}{N} \sum_{i=1}^{N} x_i$$



- $\mathrm{E}[c] = c$
- $\mathrm{E}\,[aX + bY] = a\,\mathrm{E}[X] + b\,\mathrm{E}[Y]$

Important to realize that estimates are always based on a finite dataset!
m is an estimate(!) of μ*; that is why there is a hat!*

Recall: variance

- Variance: average deviation from expected value,

$$\sigma^2 = \mathrm{var}(X) = \int_{-\infty}^{\infty} (x-\mu)^2 \, p(x) \; dx$$

or

$$\sigma^2 = \mathrm{E}[(X - \mathrm{E}(X))^2] = \mathrm{E}[X^2] - (\mathrm{E}[X])^2$$

- σ is called the standard deviation

- $\mathrm{var}(X) \geq 0$
- $\mathrm{var}(c) = 0$
- $\mathrm{var}(aX) = a^2 \, \mathrm{var}(X)$

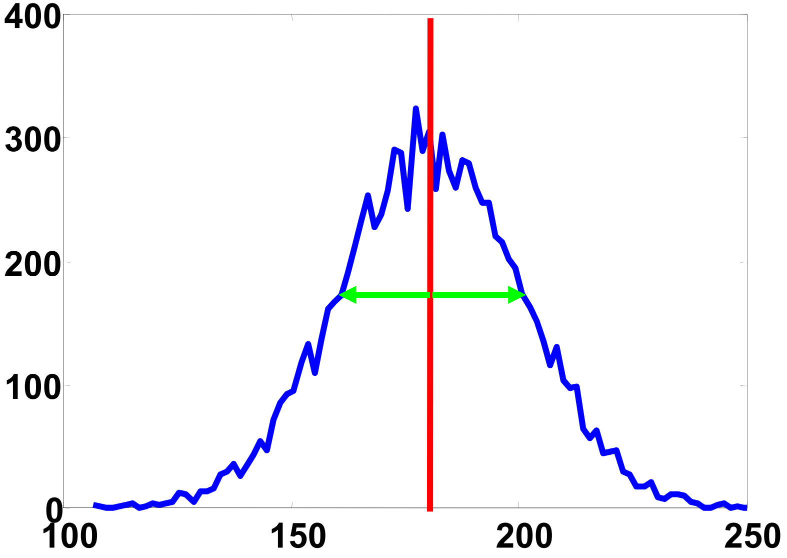
Recall: variance (2)

- Again, on data sets $\{x\}$ we can only estimate the variance:

$$s^2 = \hat{\sigma}^2 = \frac{1}{N}\sum_{i=1}^{N}(x_i - \hat{\mu})^2$$

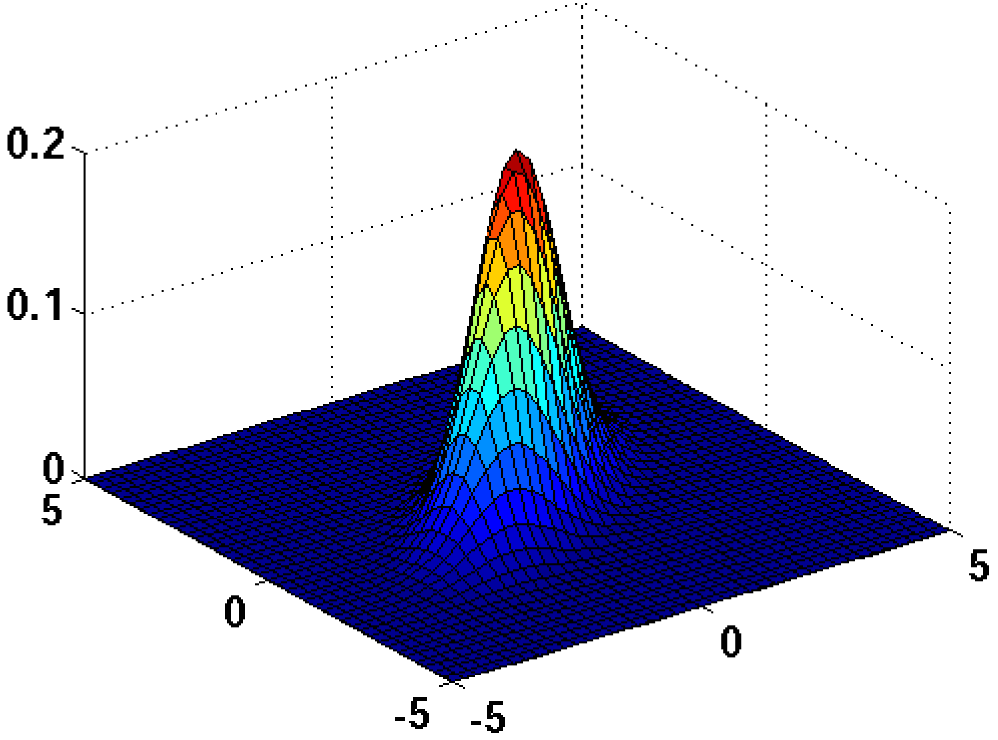
- Usually, this unbiased estimator is used:

$$s^2 = \hat{\sigma}^2 = \frac{1}{N-1}\sum_{i=1}^{N}(x_i - \hat{\mu})^2$$



Recall: joint distributions

- For $p > 1$ measurements $x = (x_1 , ..., x_p)$, joint distributions & densities:



Recall: covariance

- Covariance: measure of how two random variables vary together,

$$\begin{aligned}\mathrm{cov}(X,Y) &= \mathrm{E}[(X-\mathrm{E}(X))(Y-E(Y))] \\ &= \mathrm{E}[XY]-\mathrm{E}[X]\mathrm{E}[Y]\end{aligned}$$

- Correlation: normalised covariance,

$$\rho(X,Y) = \frac{\mathrm{cov}(X,Y)}{\sqrt{\mathrm{var}(X)\mathrm{var}(Y)}} \in [-1,1]$$

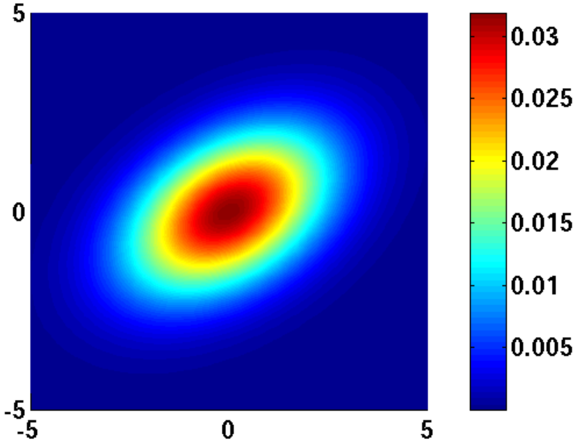
- $\mathrm{cov}(X,Y) = 0$: X and Y are uncorrelated

Recall: covariance (2)

- For a set of random variables $X_1 \ldots X_p$, we can calculate a covariance matrix,

$$\Sigma = \begin{bmatrix} \mathrm{cov}(X_1, X_1) & \mathrm{cov}(X_1, X_2) & \ldots & \mathrm{cov}(X_1, X_p) \\ \mathrm{cov}(X_{2,} X_1) & \ldots & \ldots & \mathrm{cov}(X_2, X_p) \\ \ldots & \ldots & \ldots & \ldots \\ \mathrm{cov}(X_p, X_1) & \mathrm{cov}(X_p, X_2) & \ldots & \mathrm{cov}(X_p, X_p) \end{bmatrix}$$

e.g.

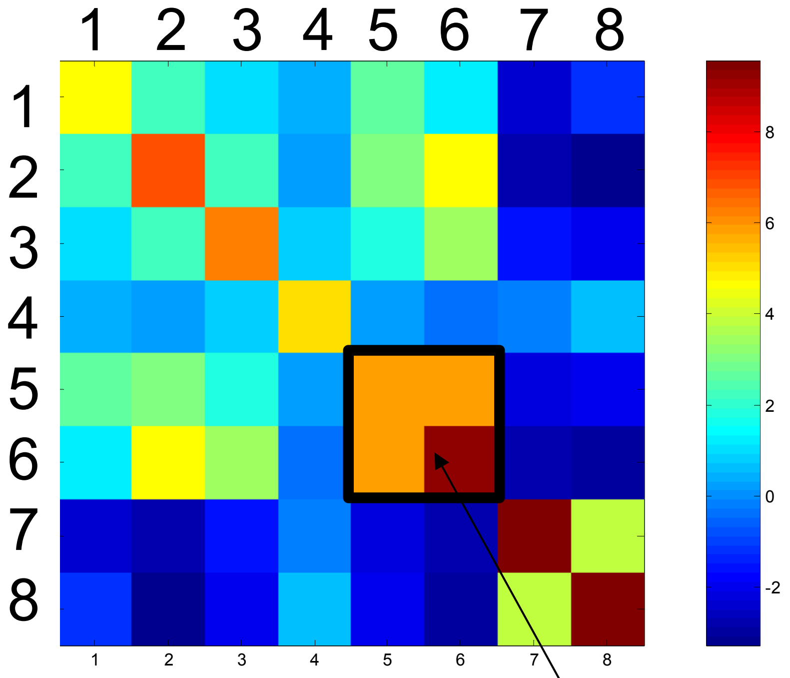


$$\longrightarrow \quad \Sigma = \begin{bmatrix} 3 & 1 \\ 1 & 2 \end{bmatrix}$$

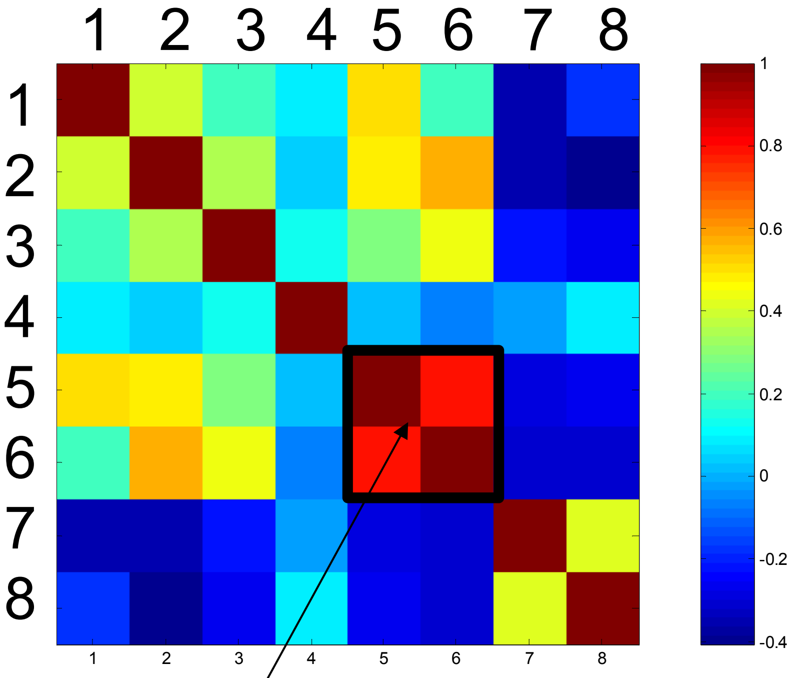
Pairwise covariance of all features!

Recall: covariance (3)

- Example: IMOX data (images of handwritten digits 1:8)



`imagesc(cov(+a))`

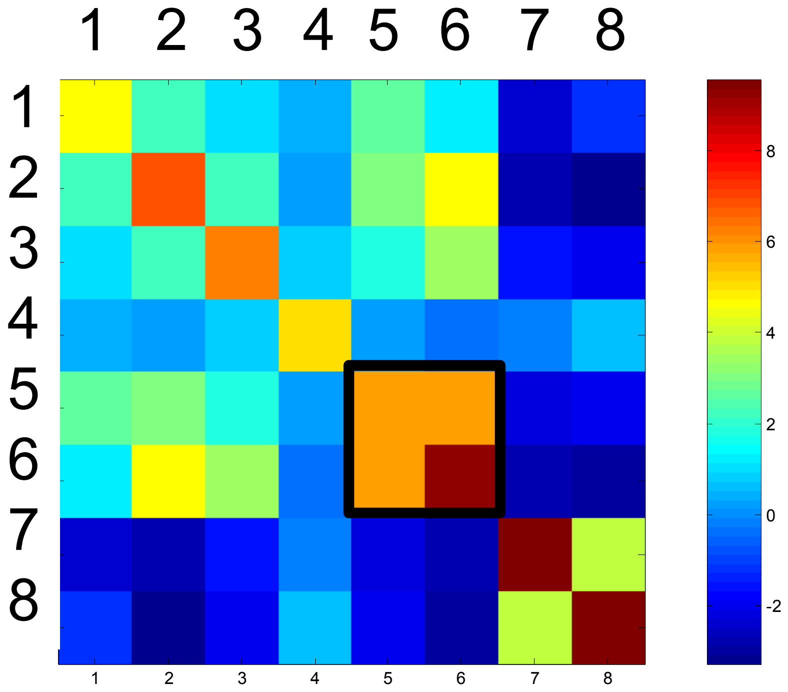


`imagesc(corrcoef(+a))`

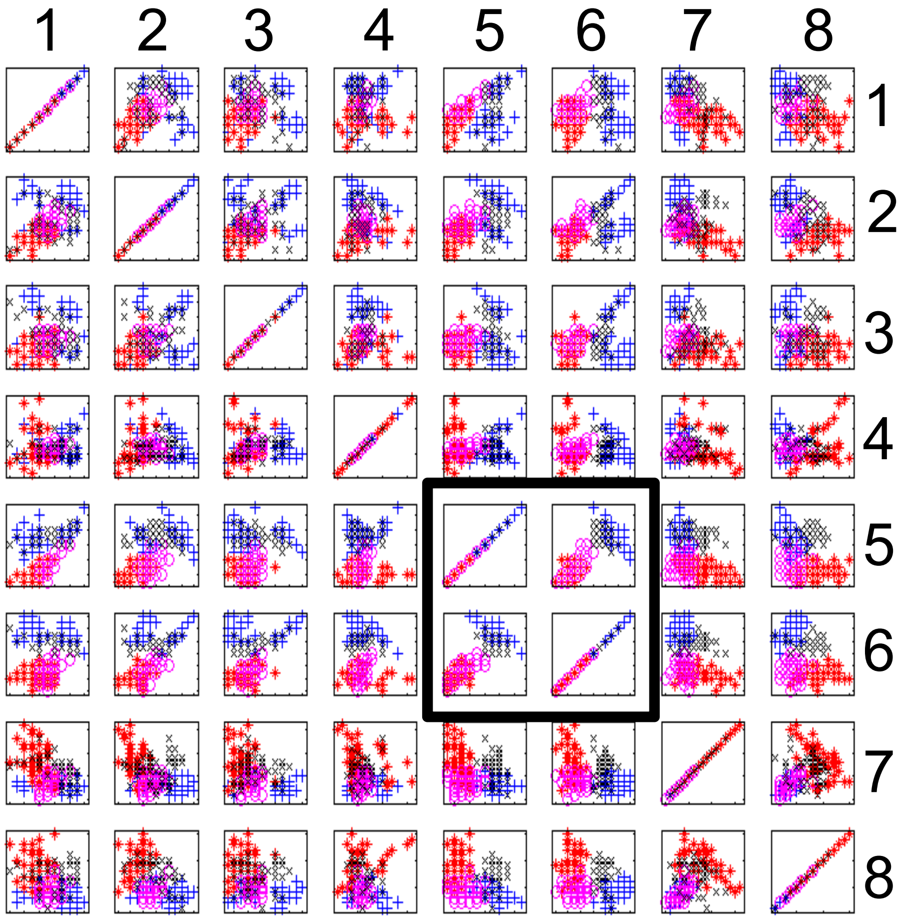
characters 5/6 are alike

Recall: covariance (4)

- Example: IMOX data



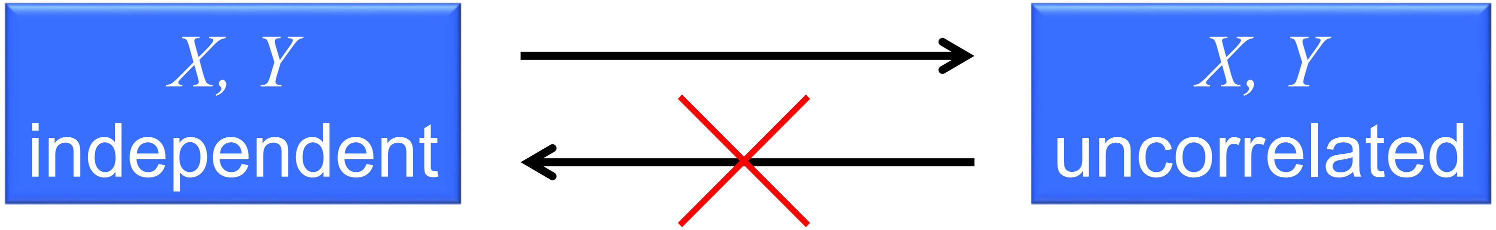
```
imagesc(cov(+a))
```



```
scatterd(a,'gridded')
```

Recall: independence

- Important concept: often needed as assumption!
- Two events A and B are independent iff
  $P(A \cap B) = P(A)\, P(B)$
- Two random variables X and Y are independent iff
  $p(x,y) = p(x)\, p(y)$



X, Y independent

X, Y uncorrelated

- Uncorrelated: “there’s no *linear* dependence”
  Independent: “there’s no dependence at all”

Recall: Bayes' theorem

- Conditional probability of A given B,

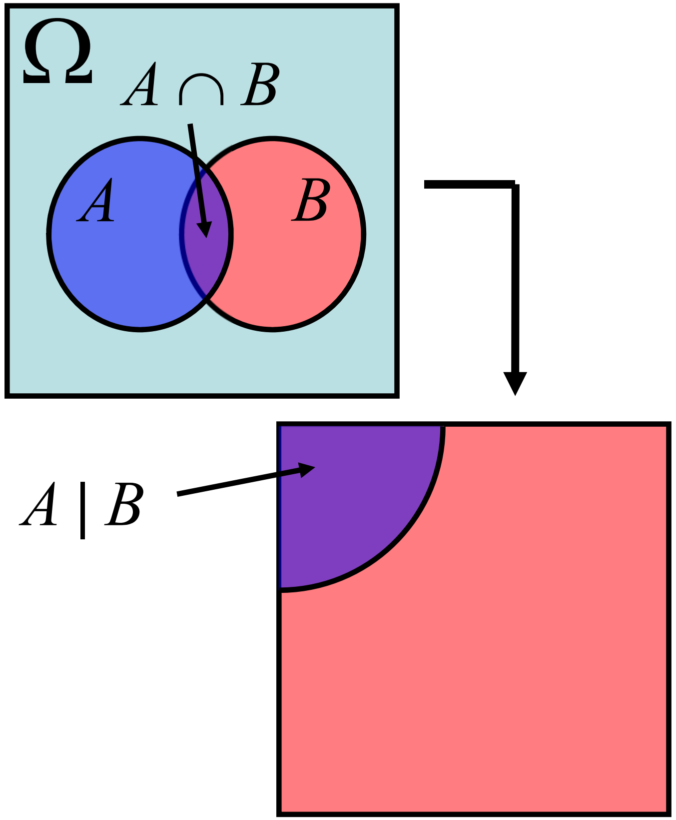
$$P(A|B) = \frac{P(A \cap B)}{P(B)}$$

- As a consequence,

$$\begin{aligned} P(A \cap B) &= P(A|B)P(B) \\ &= P(B|A)P(A) \end{aligned}$$

- Bayes' theorem:

$$P(A|B) = \frac{P(B|A)P(A)}{P(B)}$$



Bayes' theorem (2)

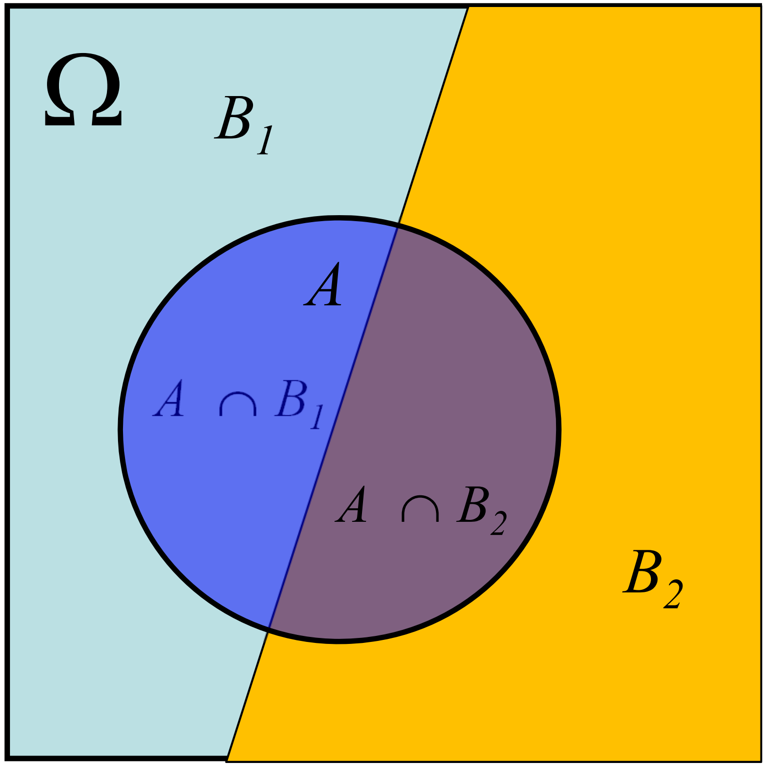
- Bayes' theorem is very useful, but controversial:
    - reverses causality
    - introduces subjective (prior) probabilities

$$P(cause \mid effect) = \frac{P(effect \mid cause)P(cause)}{P(effect)}$$

- **… but the cornerstone of pattern recognition and machine learning**
    - $P(disease|temperature) = \frac{P(temperature|disease)P(disease)}{P(temperature)}$
    - What is P (disease)? How to measure / know?

Recall: total probability

- Total probability:
- $P(A) = \sum_{\forall B_i} P(A \cap B_i)$
- $P(A) = \sum_{\forall B_i} P(A|B_i)P(B_i)$



Bayesian estimation

Bayes' theorem (3)

- In statistical learning, we want to know $p(y \mid x)$ so that we can predict (for example) the most probable output y for a given input x

- Problem: this is often very hard to model or estimate...
  - Predict gender based on height measurement: $p(\text{gender}|\text{height})$?
  - Predict fruit type based on color measurement: $p(\text{fruit}|\text{color})$?
  - Predict temperature based on thermometer reading: $p(\text{temperature}|\text{thermometer reading})$?

problem is that you need to measure too much:
***for every height** you need a number of examples of different genders*
feature = continuous & class label not

Bayes' theorem (4)

- Solution: combine probabilities
  - y = cause, outcome, target, label (ω), ...
  - x = effect, measurement, feature, ...

$$\underbrace{p(y \mid x)}_{\text{posterior probability}} = \frac{\overbrace{p(x \mid y)}^{\text{conditional probability}}\overbrace{p(y)}^{\text{prior probability}}}{\underbrace{p(x)}_{\text{normalisation}}}$$

We update our prior belief (prior) using observations (conditional)

Bayes' theorem (5)

- Classification example $p(\omega \mid \boldsymbol{x})$:
    - $\omega \in$ { 'man', 'woman' } = label
    - $x \in \mathbb{R}^1$ = height measurement(m)
- $p(\omega)$: prior probability of seeing a 'man' or a 'woman' here: ...?
- $p(x|\omega)$: density of x (height) when the person is actually a 'man' or a 'woman'

$p(x)$: density of height measurement x here (total probability):

$$p(x) = \sum_i p(x \mid \omega_i)\, p(\omega_i)$$

Issue: Prior for man/woman? In NL? In Delft? In classroom?

Bayes' theorem (6)

- Regression example $p(y \mid x)$:
  - $y \in \mathbb{R}^1$ = outside temperature (°C)
  - $x \in \mathbb{R}^1$ = thermometer measurement (°C)
- $p(y)$: prior probability of having some outside temperature y

  $p(x|y)$: density of x (measured temperature) when outside temperature is actually y
- $p(x)$: density of a certain thermometer measurement x here:

$$p(x) = \int p(x \mid y) p(y) dy$$

Again: Prior for outside temperature in NL, this month?
Realise that p(x|y) is still difficult to estimate because now y is continuous.

Bayesian estimation

- Estimate prior, $p(y)$, and conditional, $p(x|y)$
- Use this to obtain posterior, $p(y|x)$
- Construct a cost function $\Lambda(y',y)$:
  the cost of predicting y' when the true outcome is y
  - for classification: cost matrix
  - when all mistakes are equally bad:
    - $\Lambda(y',y) = 0$ when $y' = y$
    - $\Lambda(y',y) = 1$ otherwise
- Bayes risk of predicting y' for measurements x :

$$r(y' \mid x) = \int \Lambda(y', y)\, p(y \mid x) dy$$

Risk of saying y' = integral over ***all possible situations****:*
Remember total probabilty: P(r) = SUM_all_y { P(r|y)p(y) }
= SUM_all_y { P(r and y)}

Bayesian estimation (2)

- Optimal prediction:

$$\hat{y} = \arg\min_{y'} r(y' \mid x)$$
$$= \arg\min_{y'} \int \Lambda(y', y)\, p(y \mid x)\, dy$$

- Bayesian estimation: minimize overall risk

$$r^{*} = E\left[r(\hat{y} \mid x)\right] = \int r(\hat{y} \mid x)\, p(x)\, dx$$

Best prediction is the one that minimizes the risk
Best system minimizes expected risk: over all possible x's

Bayesian estimation (3)

- Example: diagnostic system
  - $\omega = \{ \text{h}, \text{d} \}$ (healthy, diseased)
  - $\Lambda(\omega',\omega) = \begin{array}{c|c|c|} & \omega = \text{h} & \omega = \text{d} \\ \hline \omega' = \text{h} & 0 & 1 \\ \hline \omega' = \text{d} & 1 & 0 \\ \hline \end{array}$
  - Say the system predicts $p(\omega = \text{d}|x) = 0.05$, then

$$r(\omega' = \text{h}|x) = \overset{0}{\Lambda(\text{h,h})}\, \overset{p(\omega=\text{h}|x)=0.95\ \text{(by definition)}}{p(\omega{=}\text{h}|x)} + \overset{1}{\Lambda(\text{h,d})}\, p(\omega{=}\text{d}|x)$$

$$= p(\omega{=}\text{d}|x) = 0.05$$

$$r(\omega' = \text{d}|x) = \Lambda(\text{d,h})\, p(\omega{=}\text{h}|x) + \Lambda(\text{d,d})\, p(\omega{=}\text{d}|x)$$

$$= p(\omega{=}\text{h}|x) = 0.95$$

  - Choose minimum risk, thus assign to h (in agreement with what you would expect by $p(\omega = \text{d}|x) = 0.05$)

Bayesian estimation (4)

- Example: diagnostic system
  - $\omega = \{\ \mathrm{h}, \mathrm{d}\ \}$ (healthy, diseased)
  - $$\Lambda(\omega',\omega) = \begin{array}{c|c|c|} & \omega = \mathrm{h} & \omega = \mathrm{d} \\ \hline \omega' = \mathrm{h} & 0 & 25 \\ \hline \omega' = \mathrm{d} & 1 & 0 \\ \hline \end{array}$$
  - Say the system predicts $p(\omega = \mathrm{d}|x) = 0.05$, then

$$r(\omega' = \mathrm{h}|x) = \Lambda(\mathrm{h,h})\, p(\omega{=}\mathrm{h}|x) + \Lambda(\mathrm{h,d})\, p(\omega{=}\mathrm{d}|x)$$

$$= 0 \cdot 0.95 + 25 \cdot 0.05 = 1.25$$

$$r(\omega' = \mathrm{d}|x) = \Lambda(\mathrm{d,h})\, p(\omega{=}\mathrm{h}|x) + \Lambda(\mathrm{d,d})\, p(\omega{=}\mathrm{d}|x)$$

$$= 1 \cdot 0.95 + 0 \cdot 0.05 = 0.95$$

  - *Realize that minimum risk now says to assign to d !*

Bayesian estimation (5)

- Cost function can have large influence on optimal decision!

- Think about:
  - Fingerprint identification (e.g. in database)
    - Cost of identifying incorrect person
  - Fingerprint verification (e.g. mobile phone)
    - Cost of incorrectly rejecting fingerprint owner
    - Cost of incorrectly allowing imposter

- Cost can often be quantified, e.g. cost of additional human intervention

Scenarios: priors and risks

- Gene expression-based data classification
  - for artefact detection
  - for generating biological hypotheses
  - for validating biological hypotheses
  - for diagnosis of the common flu
  - for diagnosis of a form of cancer
- Protein-protein interaction prediction
  - for protein complex prediction
  - for discovering signaling pathways
  - for suggesting *in vitro* experiments
  - for suggesting *in vivo* experiments
  - for drug target analysis

Recapitulation

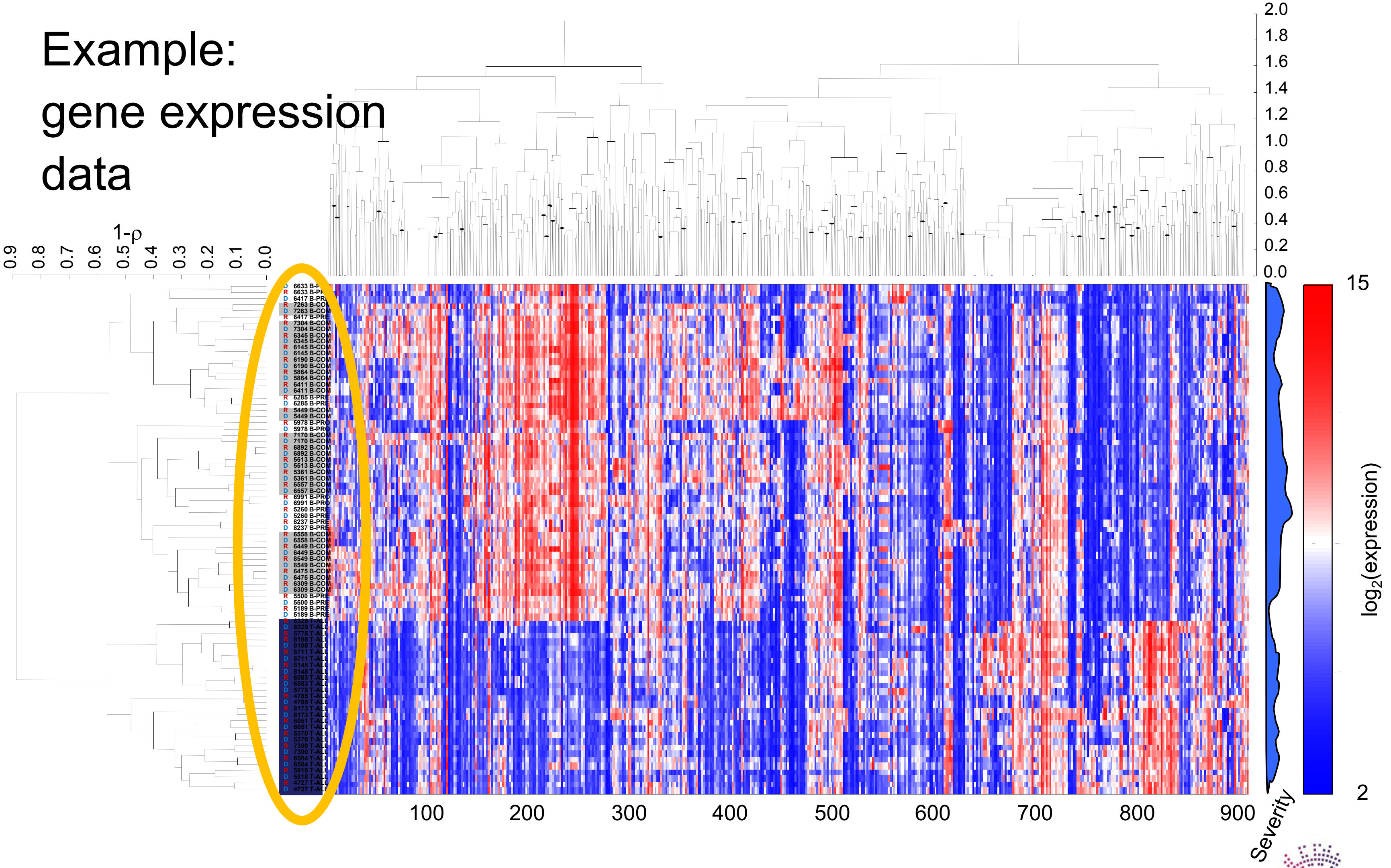
- *Machine learning* is concerned with the construction of approximate, generalizing models by learning from examples
- The *machine learning pipeline* consists of defining objects and measurements, constructing a predictive function and applying it to unseen data
- *Bayes' theorem* plays a central role in statistical machine learning
- *Bayesian estimation*
    - provides a framework for minimizing cost due to errors
    - combines class-conditional and prior distributions into posterior ones

10min break

Bayesian classification

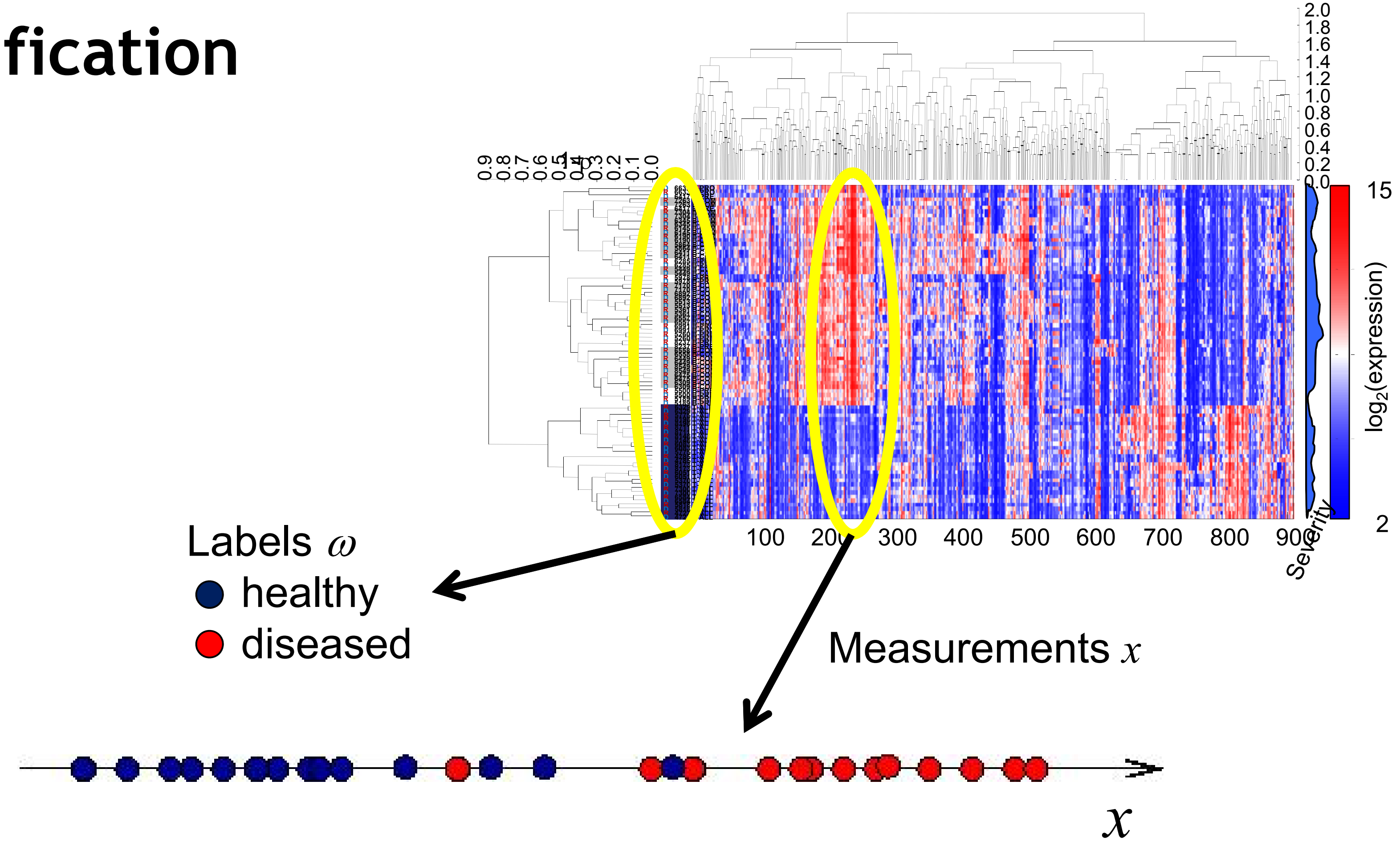
Classification in bioinformatics

- Example:
  gene expression
  data



- But again: theory applies to any type of data!

Classification



Labels ω

- ● healthy
- ● diseased

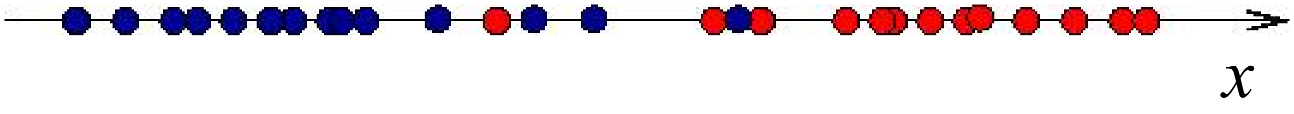
Measurements x

x

As example, consider a single gene expression measurement x

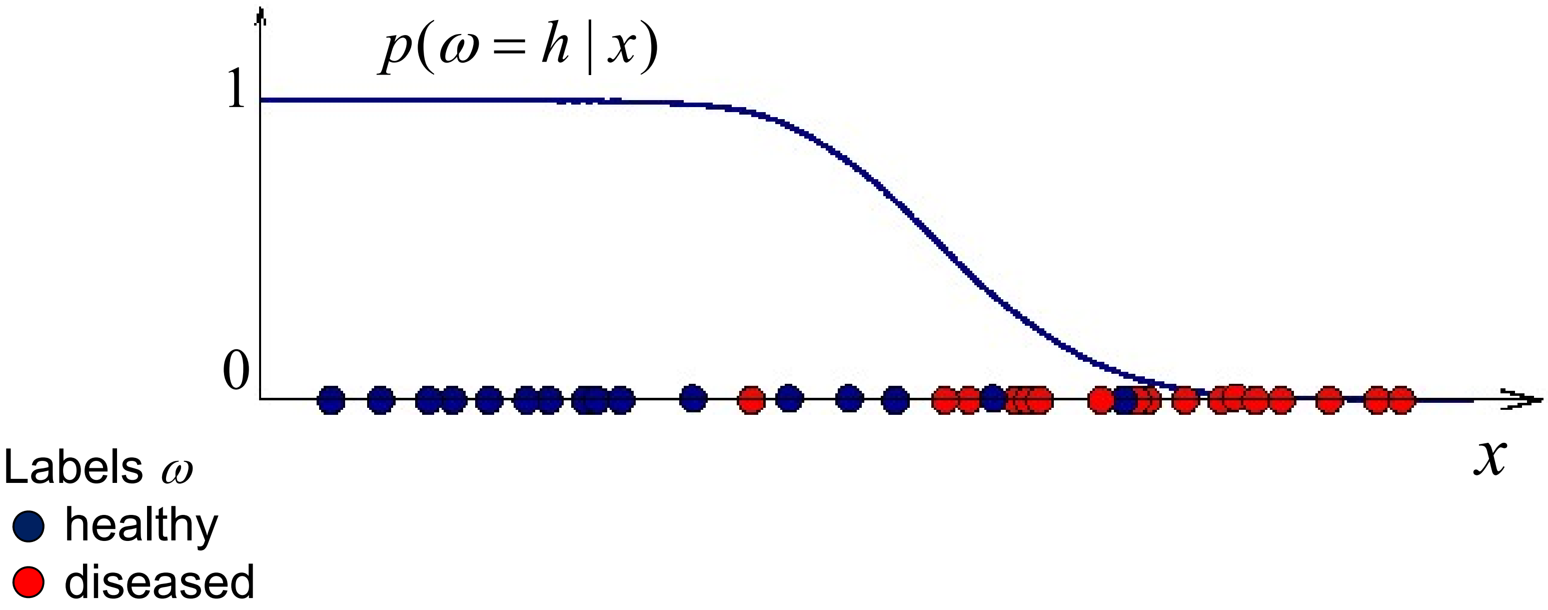
Posterior probability

- For each object, we have to estimate $p(\omega|x)$ or $p(y|x)$



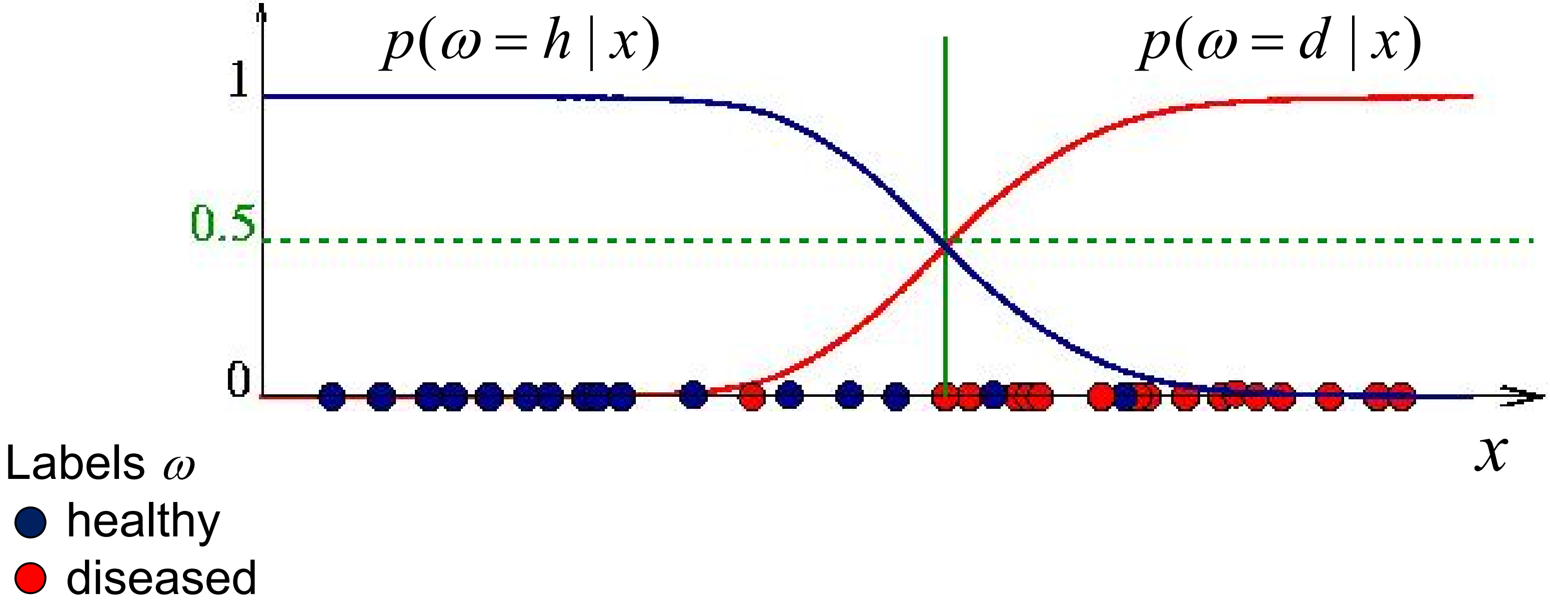
Posterior probability (2)

- For each object, we have to estimate $p(\omega|x)$ or $p(y|x)$



Posterior probability (2)

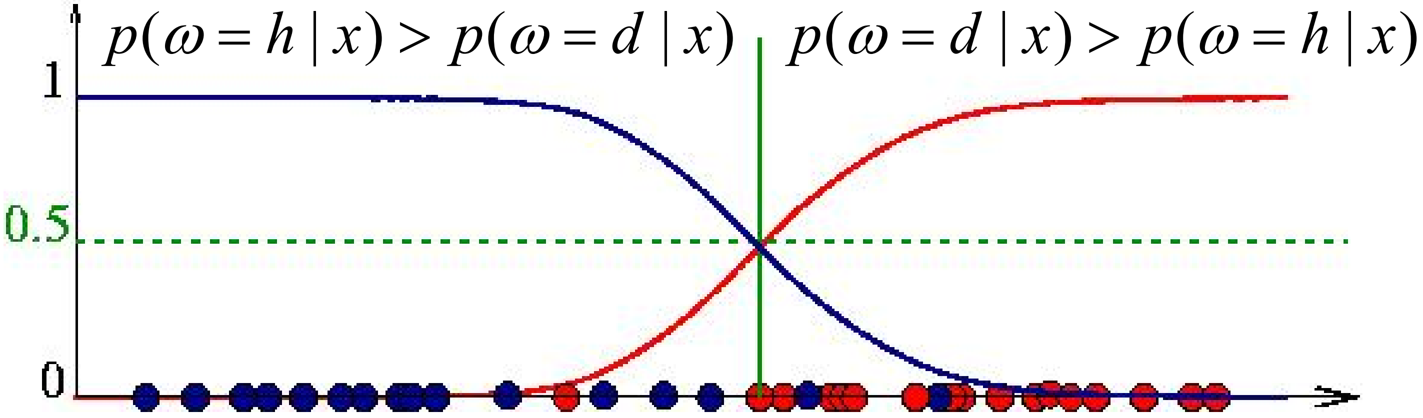
- For each object, we have to estimate $p(\omega|x)$ or $p(y|x)$



- Of course: $\sum_{c=1}^{C} p(\omega = c \mid x) = 1$

Posterior probability (3)

- For each object, we have to estimate $p(\omega|x)$ or $p(y|x)$



Labels ω

● healthy

● diseased

A classifier

- There are several ways to describe a classifier:
  - if $p(\omega = h \mid x) > p(\omega = d \mid x)$ then assign to h
    otherwise to d
  - if $p(\omega = h \mid x) - p(\omega = d \mid x) \geq 0$ then assign to h
    otherwise to d
  - if $\dfrac{p(\omega = h \mid x)}{p(\omega = d \mid x)} \geq 1$ then assign to h
    otherwise to d
  - if $\ln\left[p(\omega = h \mid x)\right] - \ln\left[p(\omega = d \mid x)\right] \geq 0$ then assign to h
    otherwise to d

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

Bayes' rule

- In many cases, the posterior is hard to estimate
- Often a certain functional form can be assumed for the *class-conditional distributions*
- Use Bayes' theorem to rewrite one into the other:
  - posterior distribution: $p(\omega = c \mid x) = \dfrac{p(x \mid \omega = c)\, p(\omega = c)}{p(x)}$
  - class-conditional distribution: $p(x \mid \omega = c)$
  - prior distribution: $p(\omega)$
  - data distribution: $p(x) = \sum_{c=1}^{C} p(x \mid \omega = c)\, p(\omega = c)$

Bayes' rule (2)

- The decision rule becomes

$$p(\omega = h \mid x) > p(\omega = d \mid x)$$

$$\Downarrow$$

$$\frac{p(x \mid \omega = h)\, p(\omega = h)}{p(x)} > \frac{p(x \mid \omega = d)\, p(\omega = d)}{p(x)}$$

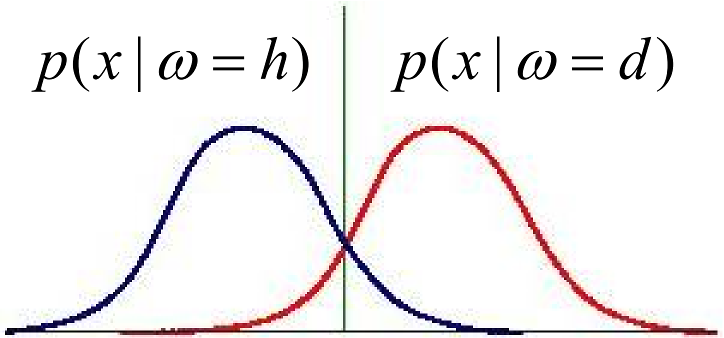
$$\Downarrow$$

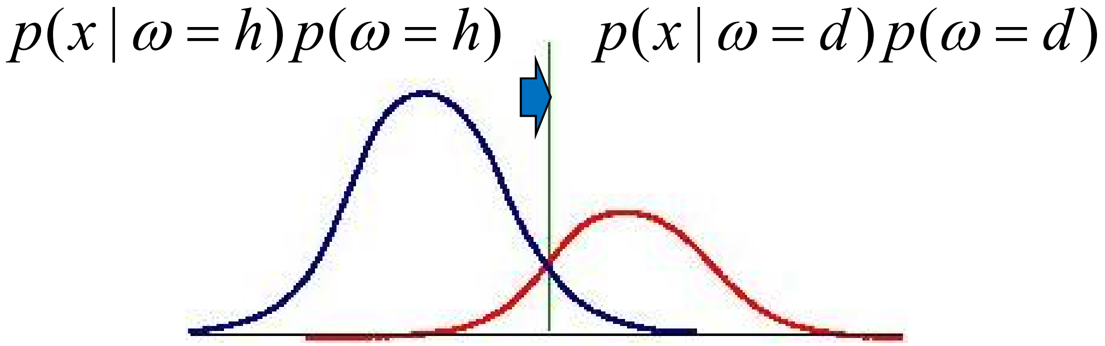
$$p(x \mid \omega = h)\, p(\omega = h) > p(x \mid \omega = d)\, p(\omega = d)$$

Seems trivial, but this is something we can measure!

Bayes' rule (3)

- The effect of the prior:

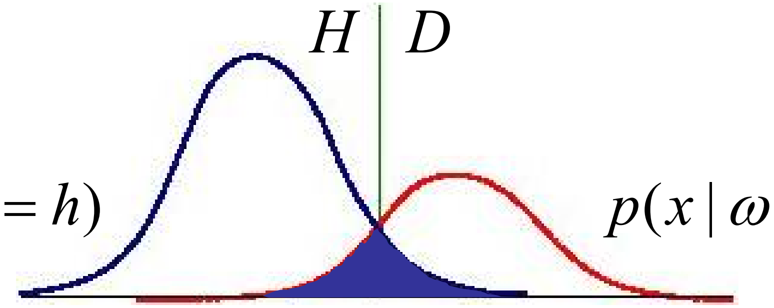




Prior can shift the decision boundary (as can risk, recall the h/d example)
If one class is very unlikely, we will not make a large error if we misclassify that class

Bayes' rule (4)

- Bayes’ error: ***minimal attainable error***
  (if data follows class-conditional contributions…)



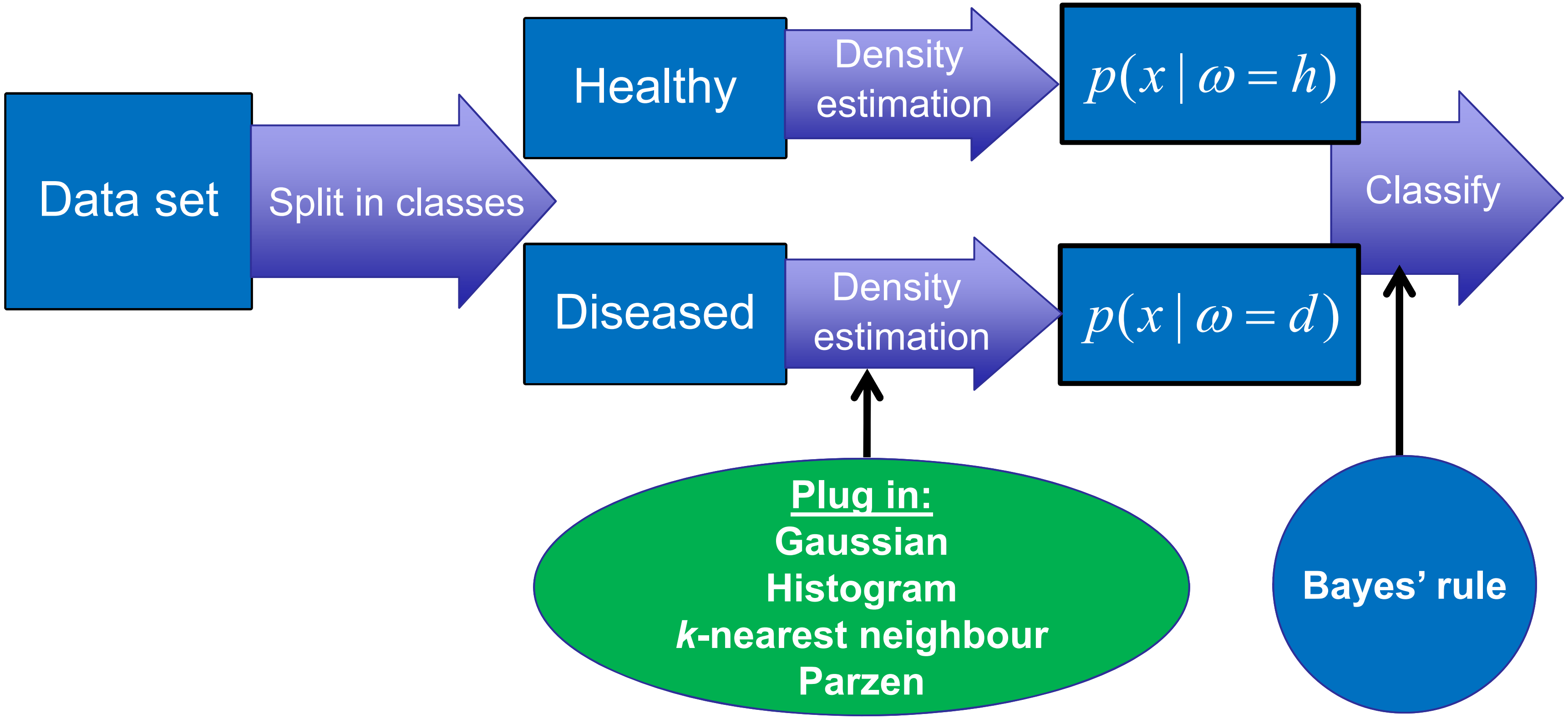
$p(x \mid \omega = h)\, p(\omega = h)$

$p(x \mid \omega = d)\, p(\omega = d)$

  - $\Lambda(\omega', \omega) = 0$ when $\omega' = \omega$
  - $\Lambda(\omega', \omega) = 1$ otherwise

Bayes' rule (5)

- In practice:



Data set

Split in classes

Healthy

Diseased

Density estimation

Density estimation

$p(x \mid \omega = h)$

$p(x \mid \omega = d)$

Classify

<u>Plug in:</u>
Gaussian
Histogram
***k*-nearest neighbour**
Parzen

Bayes' rule

Density estimation

Plug-in Bayes classifier

- Bayes' rule:

$$c_{opt} = \arg\max_c \, p(\omega = c \mid x) = \arg\max_c \, p(x \mid \omega = c)\, p(\omega = c)$$

- Given priors, we only require the class conditional distributions $p(x|\omega=c)$

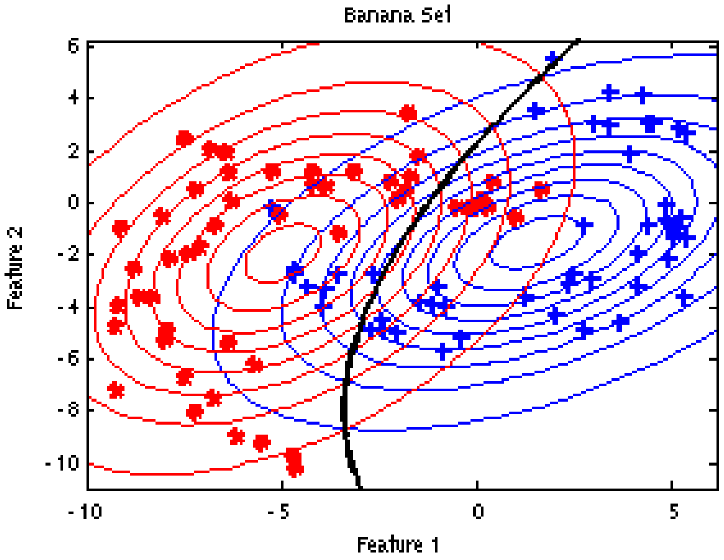
- In practice we will always have to *estimate* $p(x|\omega=c)$ by $\hat{p}(x \mid \omega = c)$ and hope that the classifier resulting when we *plug in* this approximation will still perform well

- Density estimation is a very hard problem!
- The resulting classifier will be *sub-optimal* and in general will *not* attain Bayes' error

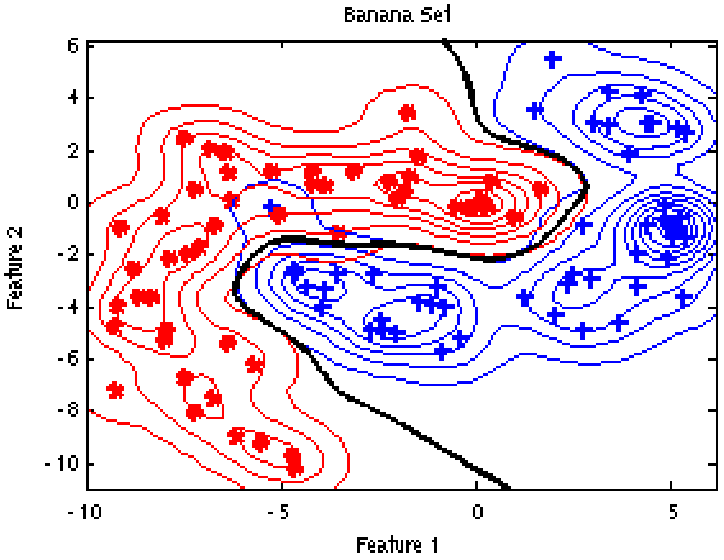
Plug-in Bayes classifier (2)

- Same problem, two different density estimates $\hat{p}(x \mid \omega = c)$

Normal density estimation



Parzen density estimation



Which one is best (Parzen)
Which one is optimal (none: true dist = normal perpendicular to two half-circles)

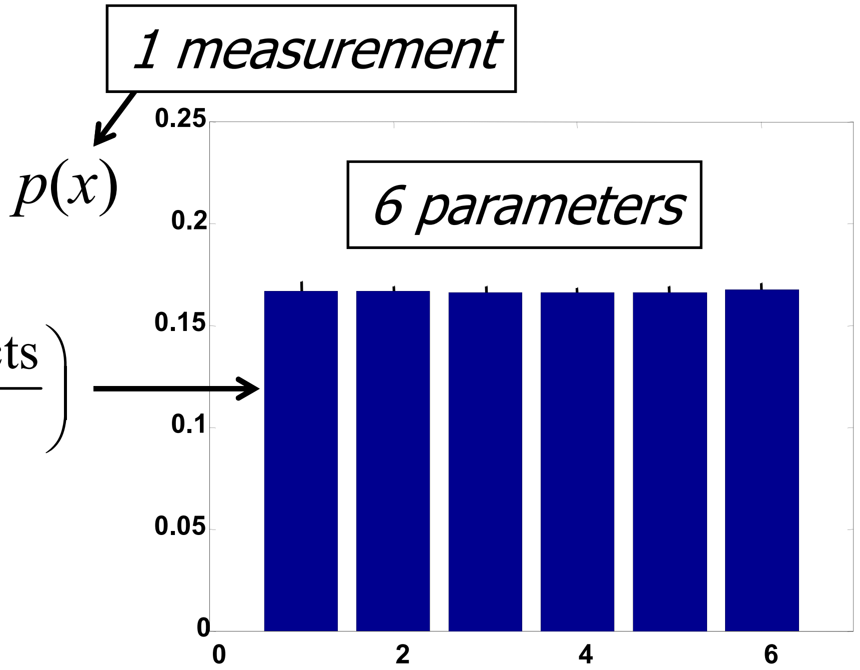
Density estimation

- Simplest approach: approximate density by histogram

  e.g. 10,000 throws
  of a dice

10,000 objects

$$\hat{p}(\mathbf{x}) = \frac{dP(\mathbf{x})}{d\mathbf{x}} = \left(\frac{\text{fraction of objects}}{\text{volume}}\right)$$



1 measurement

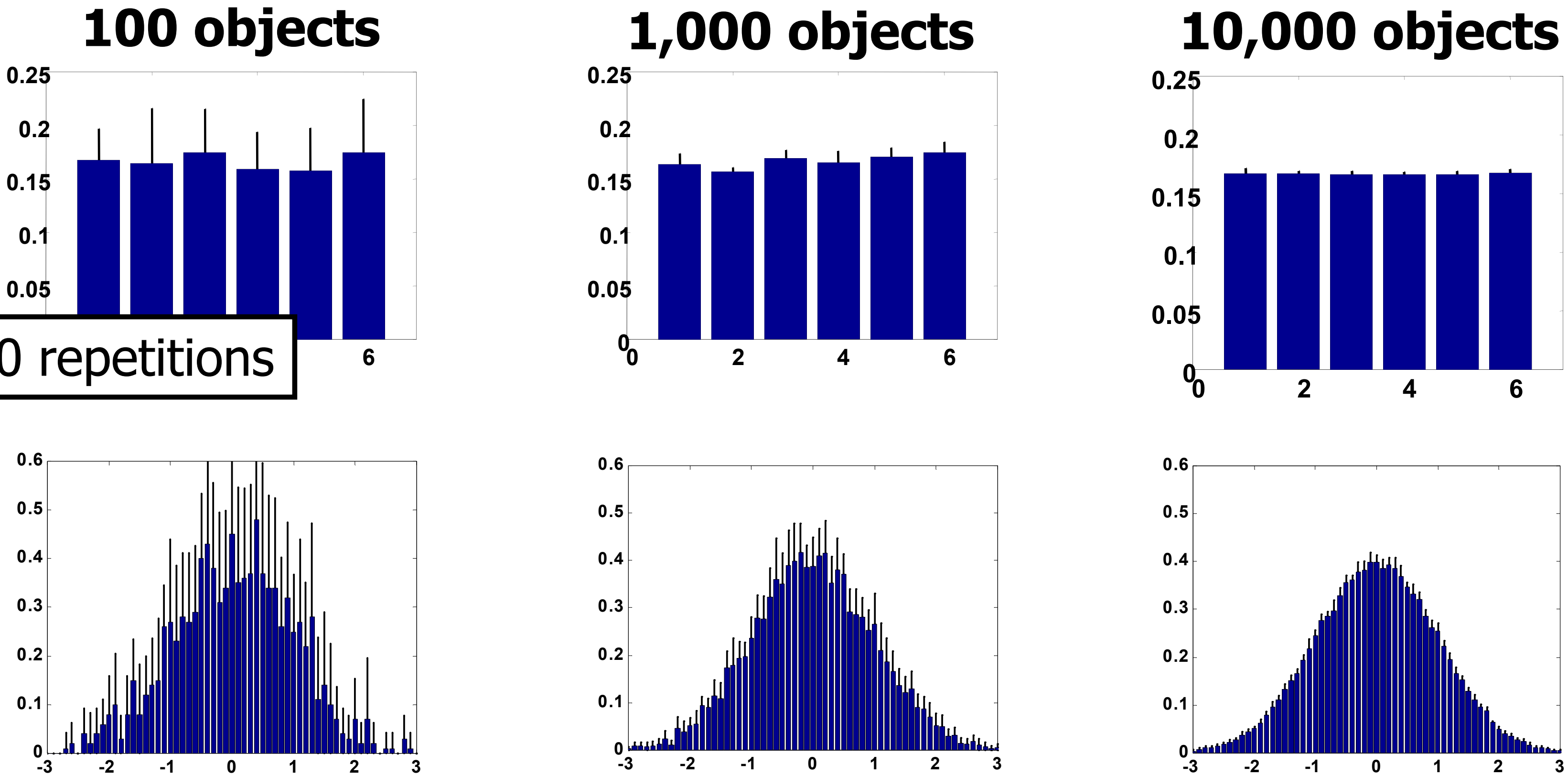
$p(x)$

6 parameters

- But...

Density estimation (2)

- Problem: accuracy



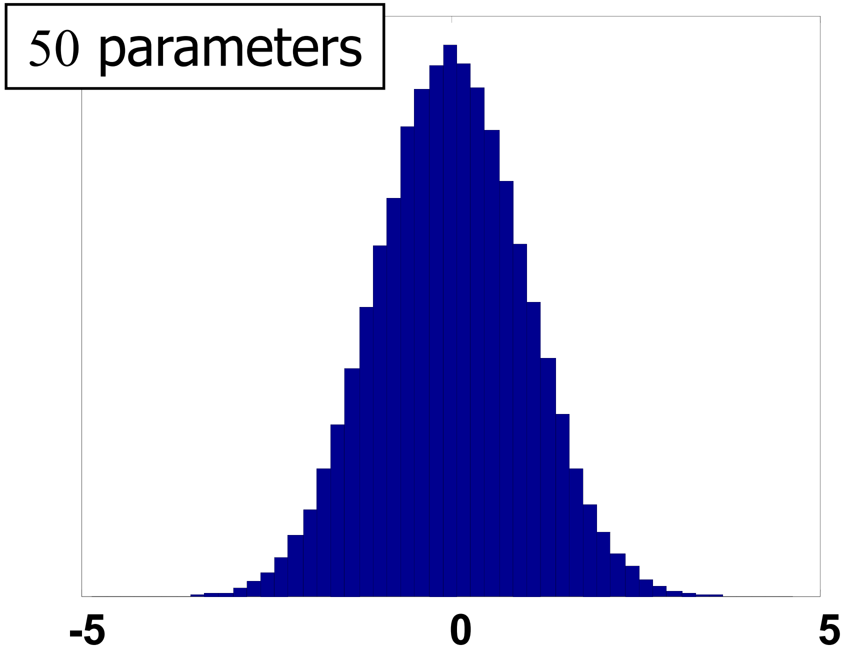
100 repetitions

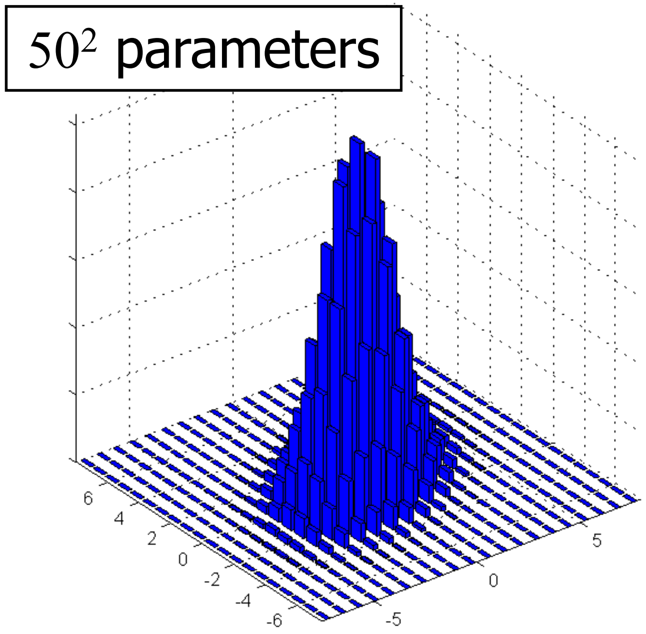
Gauss: 50 bin -> 50 parameters to estimate

Density estimation (3)

- For 1 - dimensional data, ± 1000 points needed

  For p - dimensional data, $\pm 1000^{p}$ points needed


50 parameters

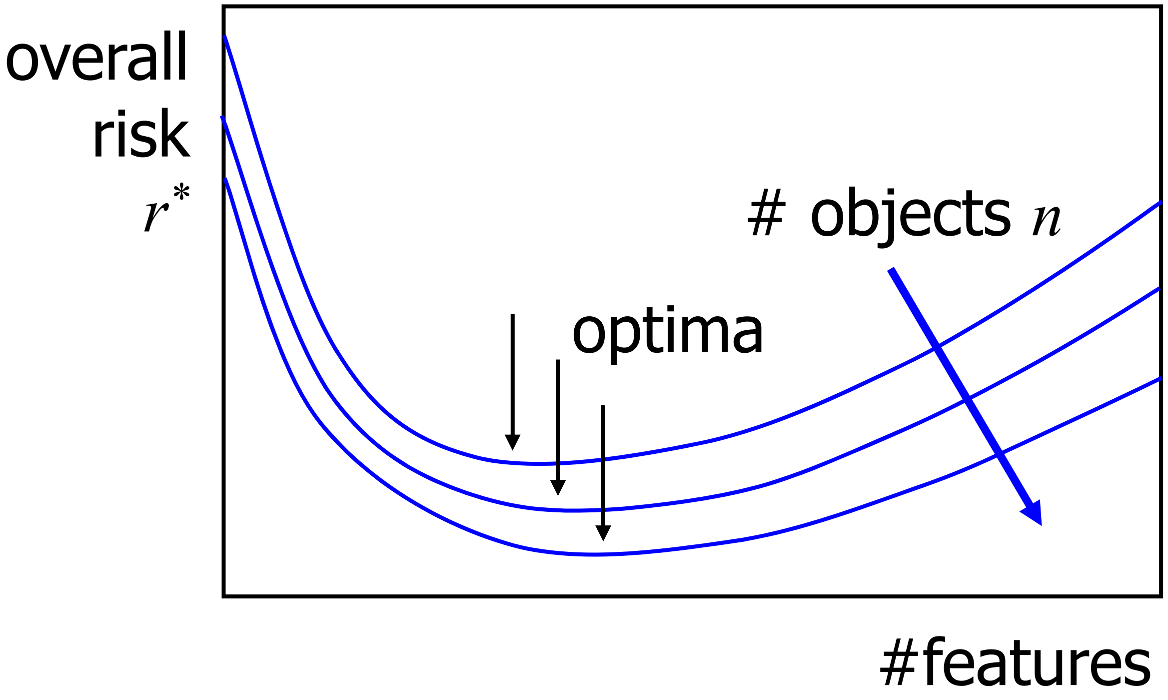

50^2 parameters

- Unworkable for $p > 2$ measurements

Curse of dimensionality

- Intuitively, using more measurements
  (e.g. width, height, color etc.) should give us
  more information about the outcome to predict
- But we never know the densities, so we have to estimate them
- The number of parameters (e.g. histogram bins)
  to estimate increases with the number of measurements
- To estimate these well, you need more objects
- Consequence:
  there is an optimal number of measurements to use

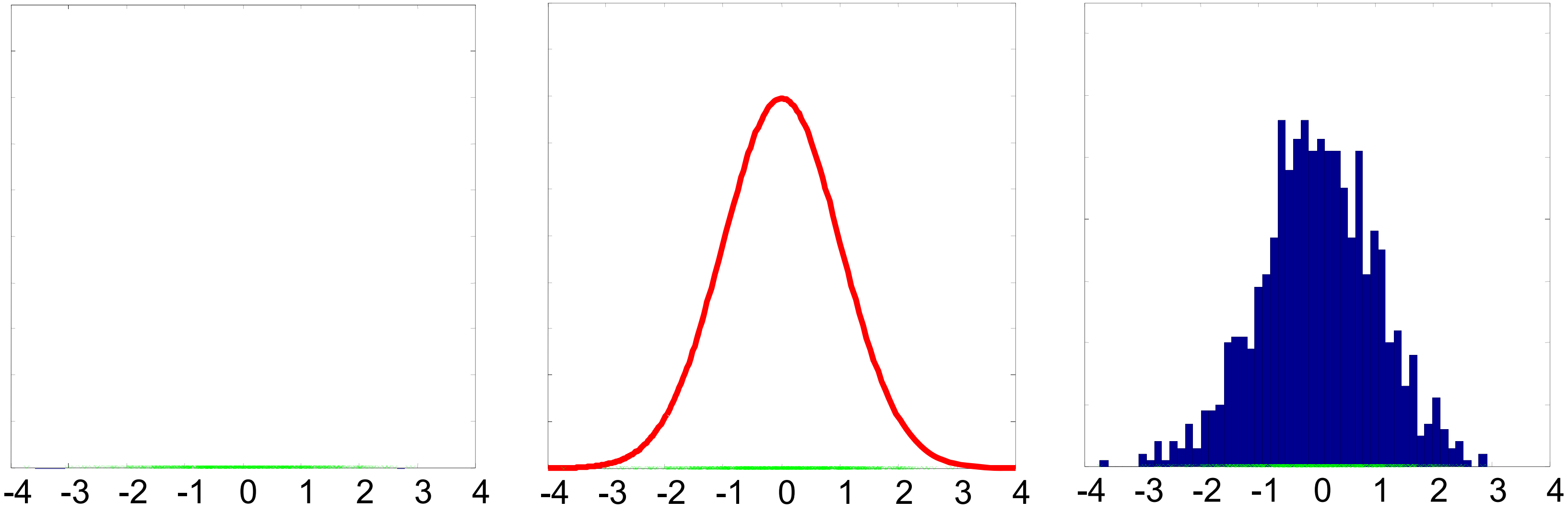
Curse of dimensionality (2)



So, realize if n -> INF than you can have many features

Density estimation (4)

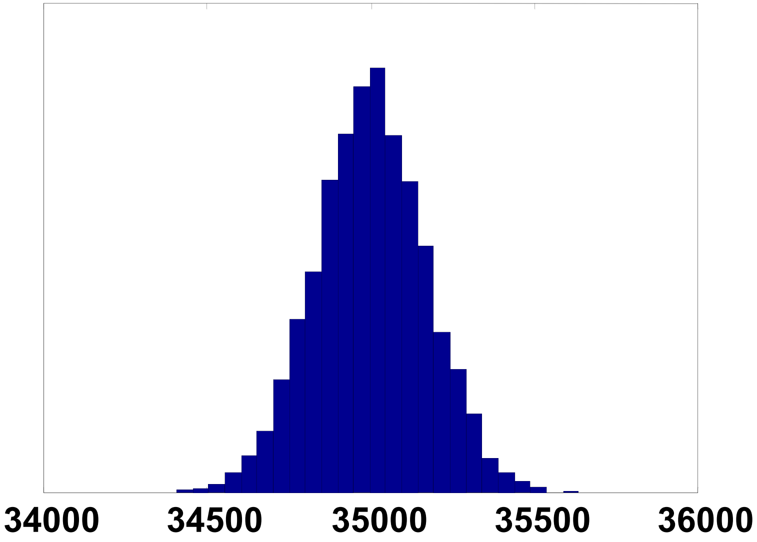
- Two main approaches:
  - *parametric*: assume simple *global* model, e.g. Gaussian, and estimate its parameters
  - *non-parametric:* assume simple *local* model, e.g. uniform, Gaussian, and aggregate



The Gaussian distribution

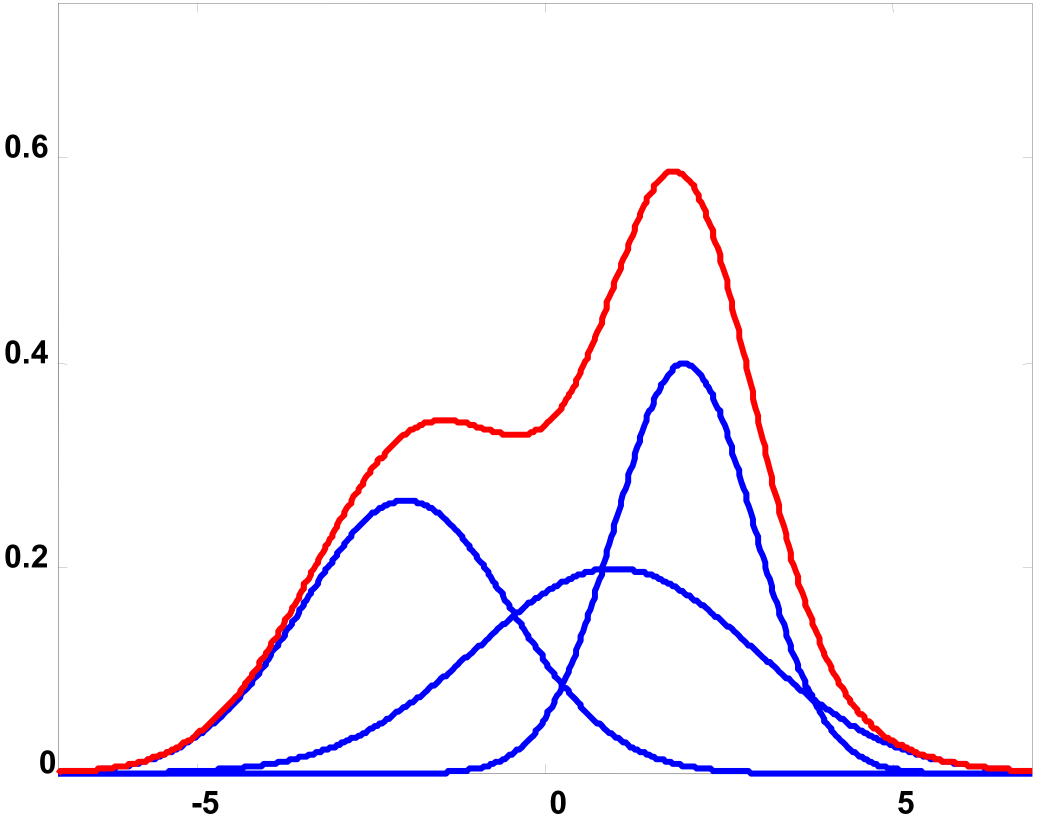
- Why Gaussians?
  - Special distribution: the Central Limit Theorem says that sums of large numbers of i.i.d. (independent, identically distributed) random variables will have a Gaussian distribution
  - Simple, few parameters
  - Often occurs in real life

    e.g. sum of eyes of
    10,000 dice throws
    (expectation = 3.5 per throw)



The Gaussian distribution (2)

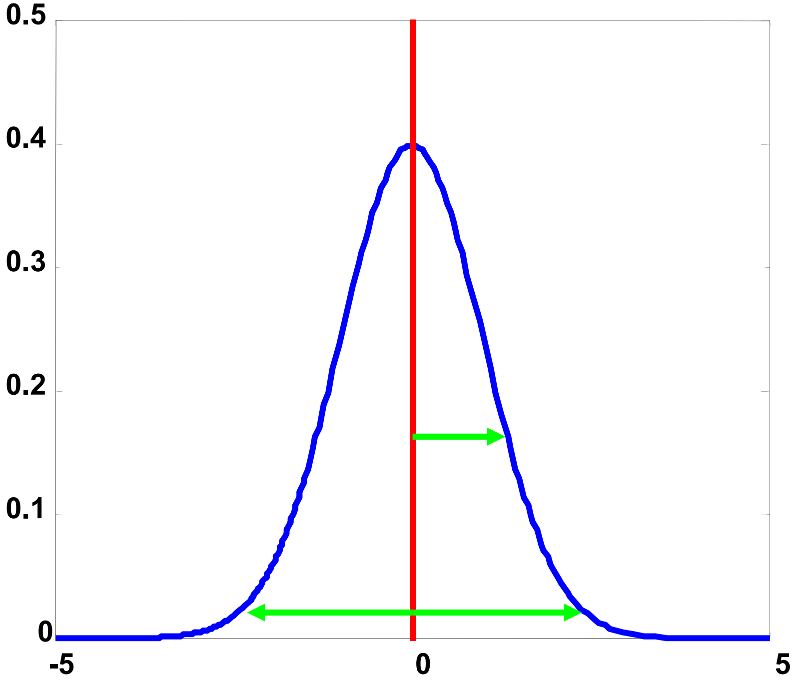
- Not necessarily too restrictive: mixture models (discussed later)



🟦 Gaussian

🟥 Mixture of Gaussians

The Gaussian distribution (3)

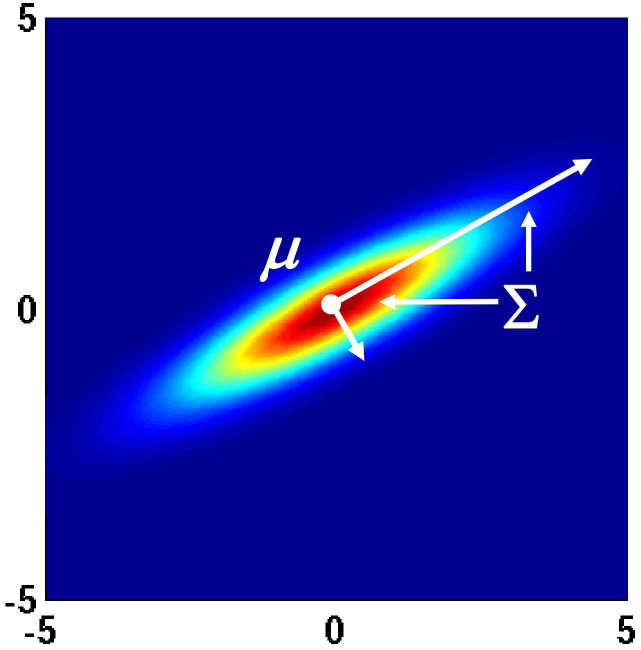


- Normal distribution = Gaussian distribution
- Standard normal distribution: $\mu = 0,\ \sigma^2 = 1$
- 95.45% of data between $[\ \mu - 2\sigma,\ \mu + 2\sigma\ ]$ (in 1D!)

- 1-dimensional density:

$$p(x) = \frac{1}{\sqrt{2\pi\sigma^2}} \exp\left(-\frac{1}{2} \frac{(x-\mu)^2}{\sigma^2} \right)$$

Multivariate Gaussian distribution

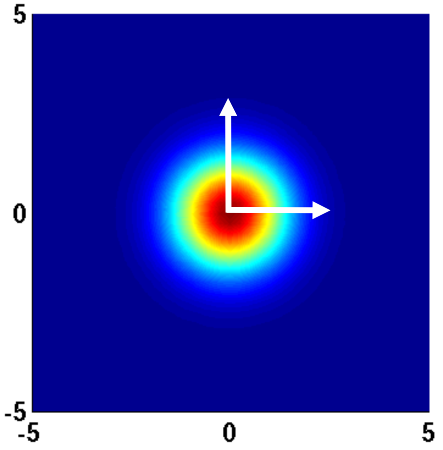


$$\Sigma = \begin{bmatrix} 3 & 1\tfrac{1}{2} \\ 1\tfrac{1}{2} & 2 \end{bmatrix}$$

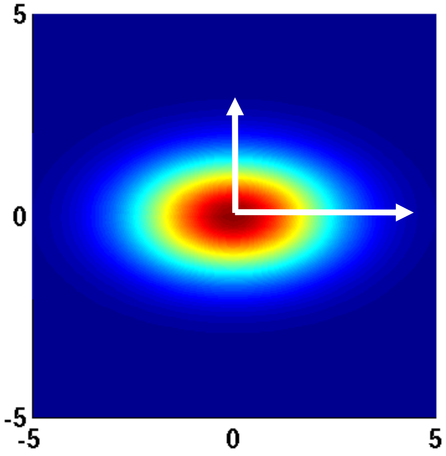
- p - dimensional density:

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

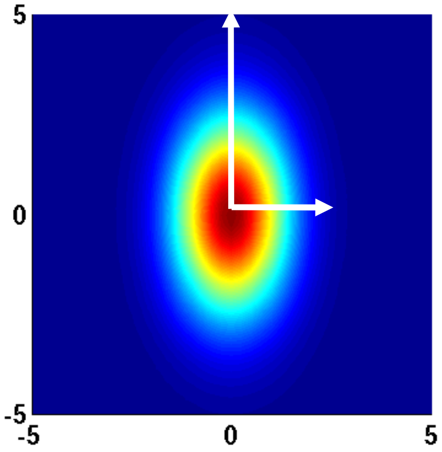
Multivariate Gaussian distribution (2)



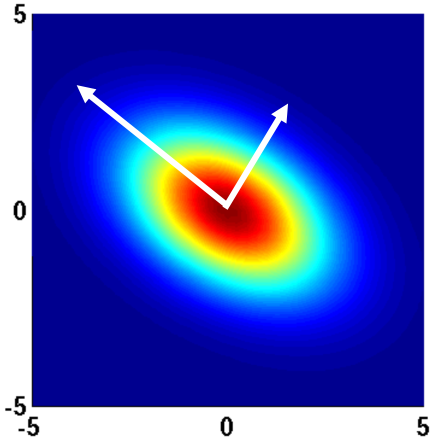
$$\Sigma = \begin{bmatrix} 1 & 0 \\ 0 & 1 \end{bmatrix}$$



$$\Sigma = \begin{bmatrix} 3 & 0 \\ 0 & 1 \end{bmatrix}$$



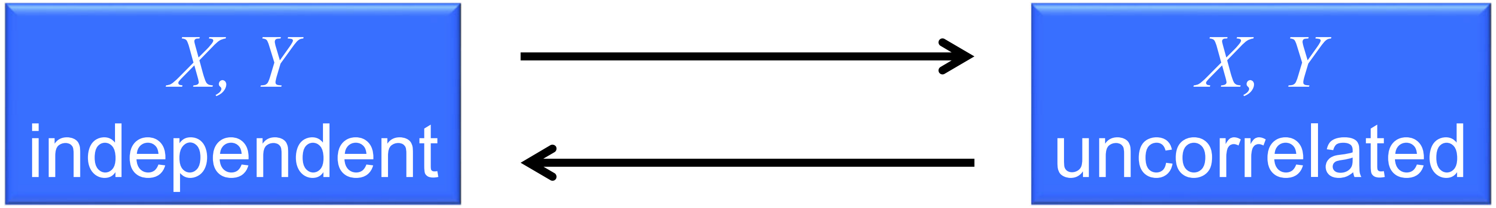
$$\Sigma = \begin{bmatrix} 1 & 0 \\ 0 & 3 \end{bmatrix}$$



$$\Sigma = \begin{bmatrix} 3 & -1 \\ -1 & 1 \end{bmatrix}$$

Special properties

- The Gaussian distribution is a special case:



X, Y independent

X, Y uncorrelated

- Proof: if uncorrelated, Σ is diagonal ($\sigma_1 \ldots \sigma_p$)

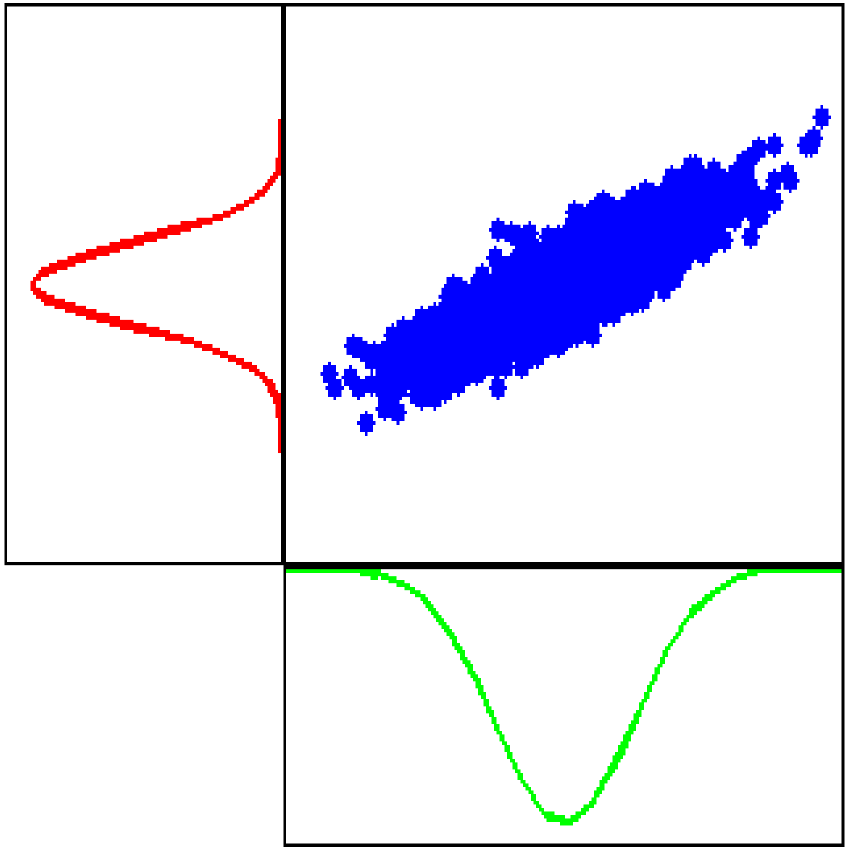
$$p(\boldsymbol{x}) = \frac{1}{\sqrt{2\pi^p \det(\Sigma)}} \exp\left(-\frac{1}{2} (\boldsymbol{x} - \boldsymbol{\mu})^{\mathrm{T}} \Sigma^{-1} (\boldsymbol{x} - \boldsymbol{\mu}) \right)$$

$$= \frac{1}{\sqrt{2\pi\sigma_1^2}} \exp\left(-\frac{1}{2} (x_1 - \mu_1)^{\mathrm{T}} \sigma_1^{-2} (x_1 - \mu_1) \right) \times \frac{1}{\sqrt{2\pi\sigma_2^2}} \exp\left(-\frac{1}{2} (x_2 - \mu_2)^{\mathrm{T}} \sigma_2^{-2} (x_2 - \mu_2) \right)$$

$$\times \ldots \times \frac{1}{\sqrt{2\pi\sigma_p^2}} \exp\left(-\frac{1}{2} (x_p - \mu_p)^{\mathrm{T}} \sigma_p^{-2} (x_p - \mu_p) \right) = p(x_1) p(x_2) \ldots p(x_p)$$

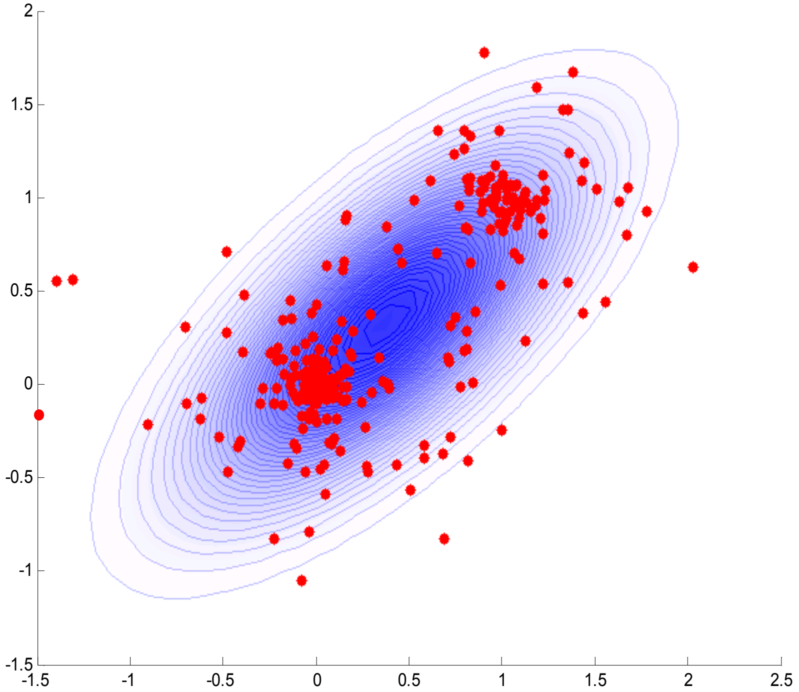
Special properties (2)

- Any projection of a high-dimensional Gaussian is itself again Gaussian



Parametric estimation

- Assume model, e.g. Gaussian and estimate mean μ and covariance Σ from data
- Sounds simple, but for p - dimensional data set:
  - μ : vector with p elements
  - Σ : matrix with $0.5\,p(p+1)$ elements
- Number of parameters increases quadratically with p : need *a lot* of data for high-dimensional problems

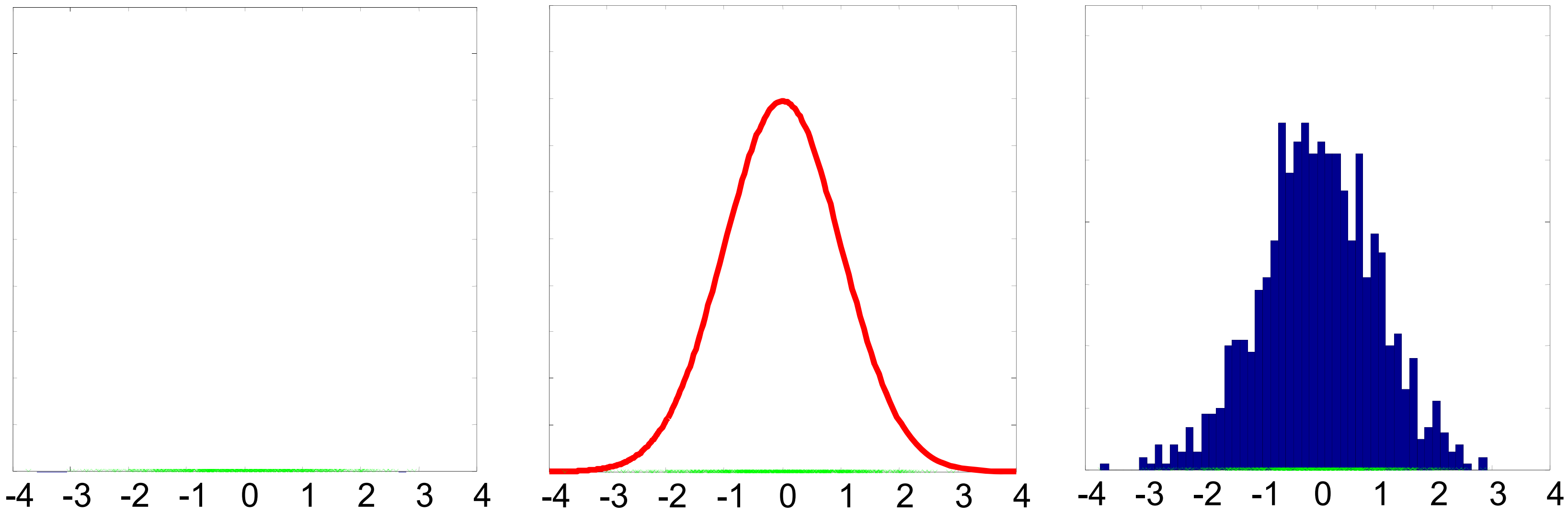


BioSB
research school

10min break

Density estimation (4)

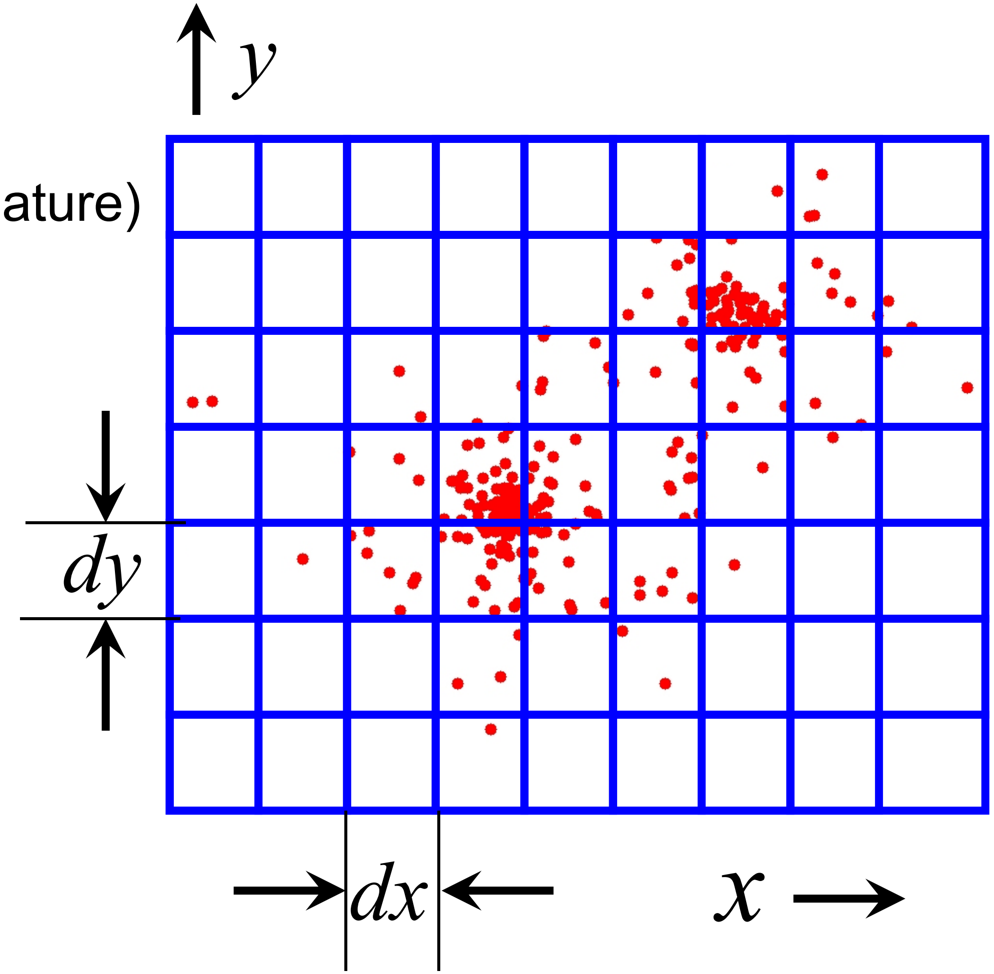
- Two main approaches:
  - *parametric*: assume simple *global* model, e.g. Gaussian, and estimate its parameters
  - *non-parametric:* assume simple *local* model, e.g. uniform, Gaussian, and aggregate



Histogramming

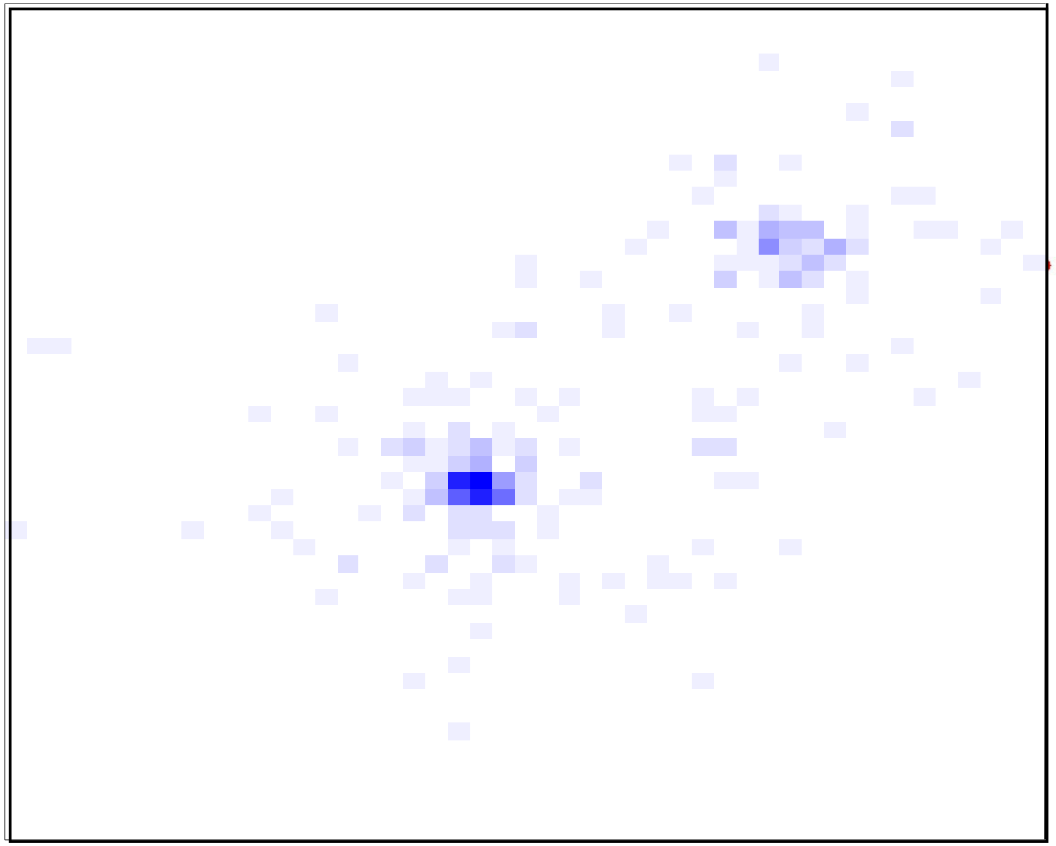
- Histogram method:
  - Divide feature space into N^p bins (*N* bins per feature)
  - Count number of objects in each bin
  - Normalize:

$$\hat{p}(\boldsymbol{x}) = \frac{n_i}{\sum_{i=1}^{N^p} n_i dx dy}$$



Histogramming (2)

- For example, using $N=50$ bins per dimension

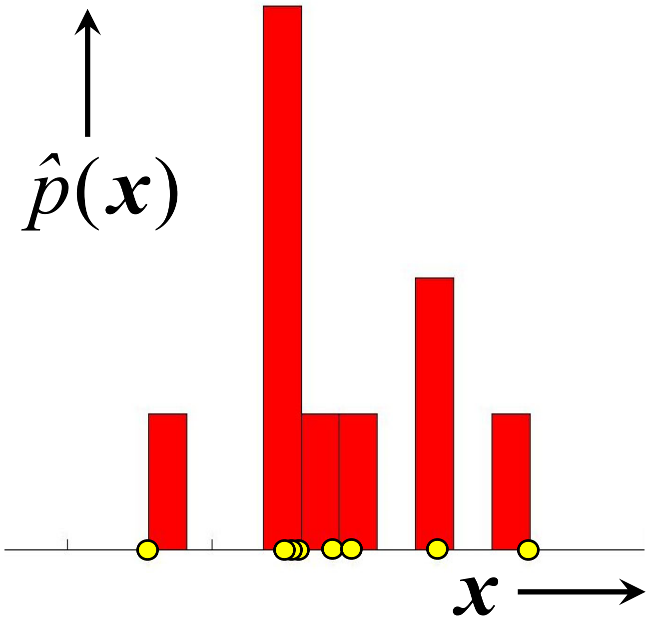


Histogramming (3)

- Histogram density estimate:

$$\hat{p}(\boldsymbol{x} \mid dx) = \left(\frac{\text{fraction of objects}}{\text{volume}} \right)$$

  - Fix cell size (dx)
  - Count #objects per cell

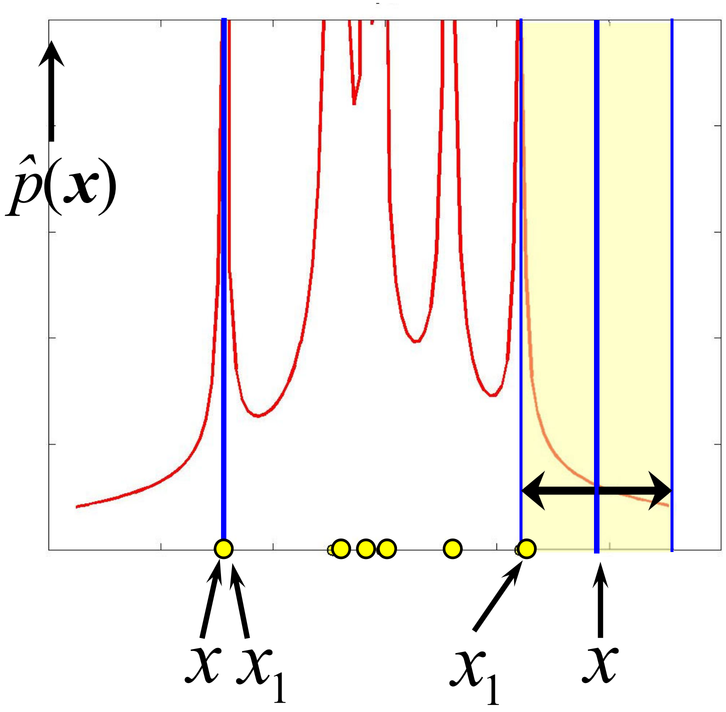


k-nearest neighbor density estimation

- *k*-nearest neighbor estimate:

$$\hat{p}(\boldsymbol{x}\,|\,k) = \left(\frac{\text{fraction of objects}}{\text{volume}}\right)$$

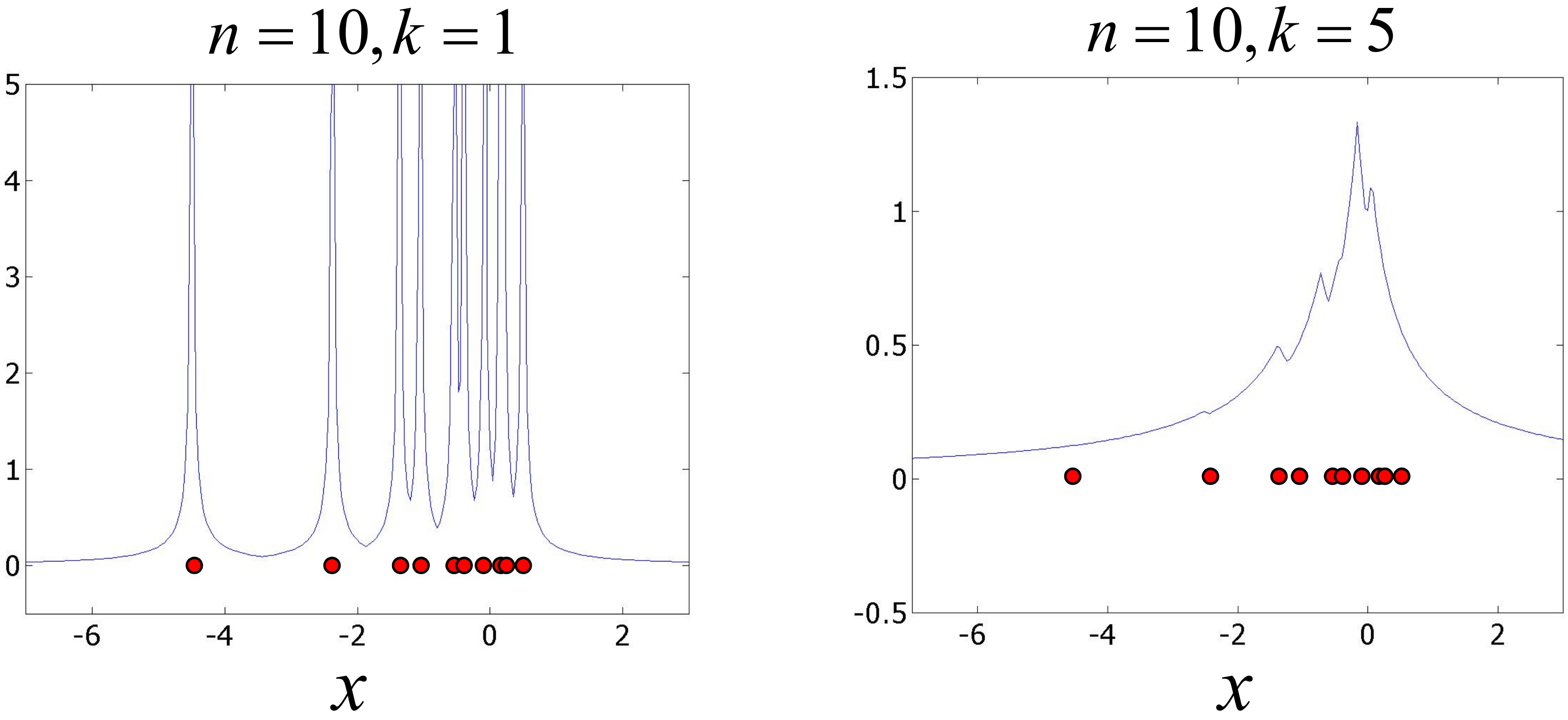
$$= \frac{k}{n\Delta x_k} = \frac{k}{n\|x - x_k\|}$$



  - Fix #objects per cell (k)
  - Determine cell size (volume)

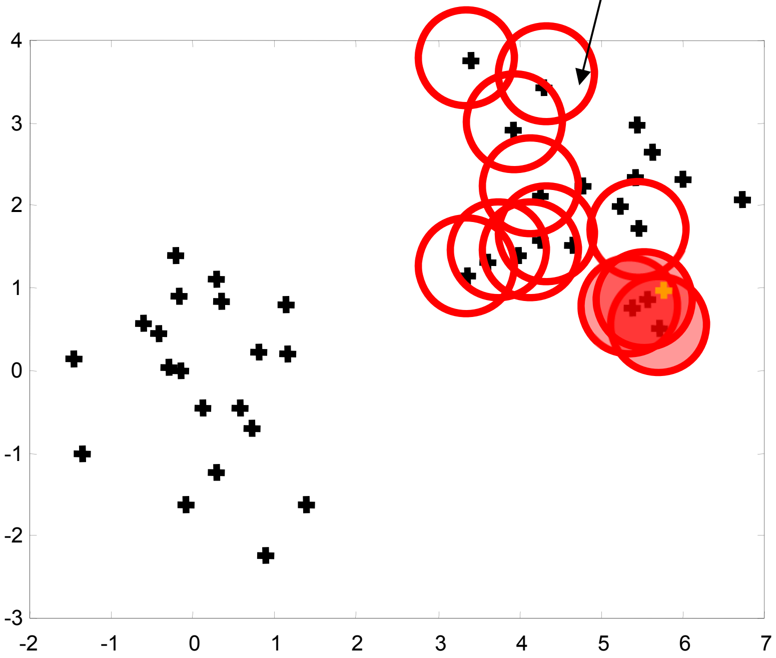
k-nearest neighbor density estimation (2)

- The density estimate for $k = 1$ contains singularities:



Parzen density estimation

Also known as Kernel-based density estimation



- Procedure:
  - Fix volume of cell
  - Vary positions of cells
  - Add contributions of cells
- Define cell shape (kernel), e.g. uniform

$$K(r,h)=\begin{cases} 0 & \text{if } |r|>h \\ 1/V & \text{if } |r|\le h \end{cases}$$

(with V the volume of the kernel)

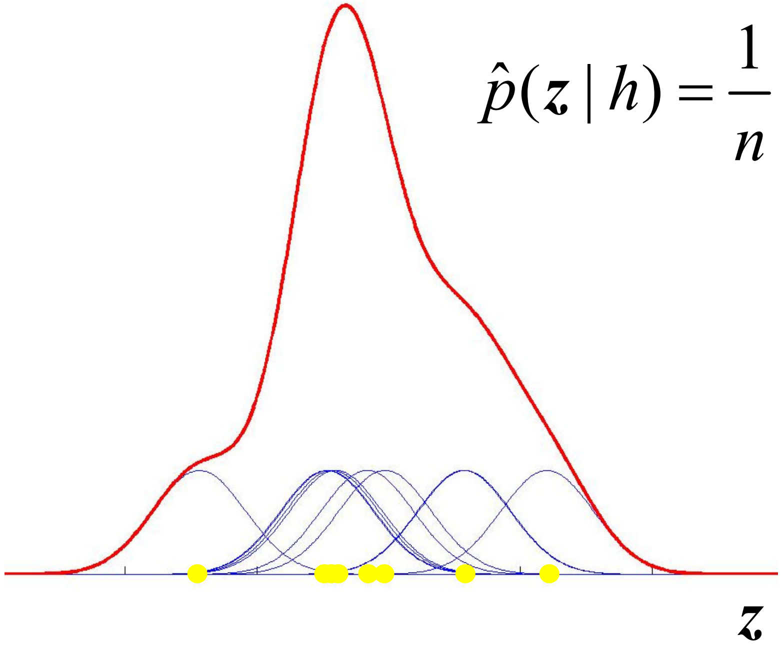
or Gaussian

- For test object z, sum all cells: $\hat{p}(z\,|\,h)=\frac{1}{n}\sum_{i=1}^{n}K\left(\|z-x_i\|,h\right)$

Parzen density estimation (2)

- With Gaussian kernel: $K(r,h) = \frac{1}{2\pi^{1/2}h}\exp\left(-\frac{1}{2}\frac{r^2}{h^2}\right)$

$$\hat{p}(\boldsymbol{z}\mid h) = \frac{1}{n}\sum_{i=1}^{n} K\left(\left\|\boldsymbol{z}-\boldsymbol{x}_i\right\|, h\right)$$

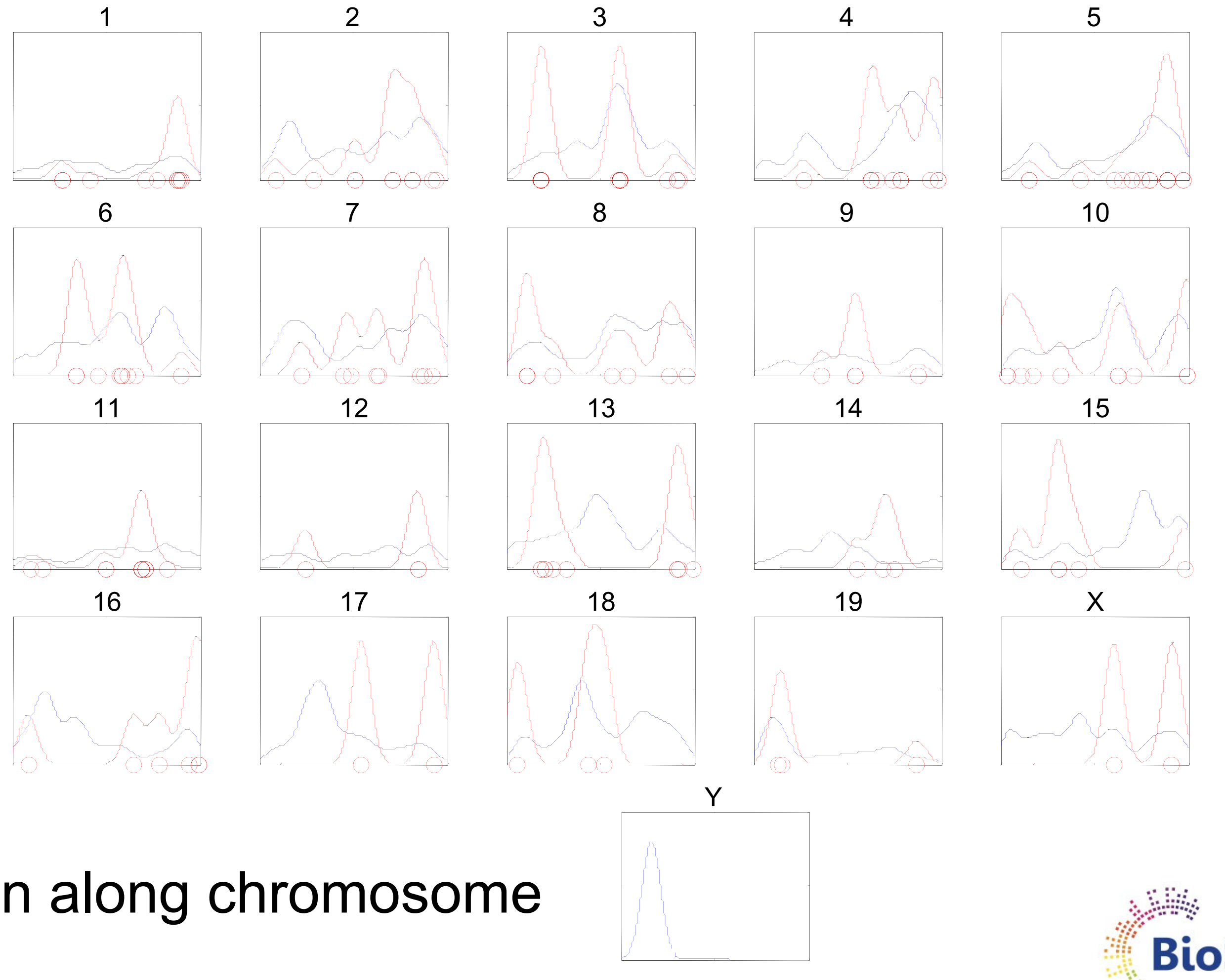


Parzen density estimation (3)

- Example: viral insertions in each chromosome

— Density of highly expressed genes

— Density of viral insertions



- Feature: position along chromosome

Parzen density estimation (4)

- Maximum likelihood (ML) estimate: choose kernel width h such that the probability of the observed data is maximal
  - PDF of observing a point $\boldsymbol{z}$:

$$\hat{p}(\boldsymbol{z} \mid h) = \frac{1}{n} \sum_{i=1}^{n} K\left(\left\| \boldsymbol{z} - \boldsymbol{x}_i \right\|, h \right)$$

  - PDF of observing dataset $\boldsymbol{x}_1, \ldots, \boldsymbol{x}_n$ (likelihood):

$$\hat{p}(X|h) = \prod_{i-1}^{n} \hat{p}(x_i|h)$$

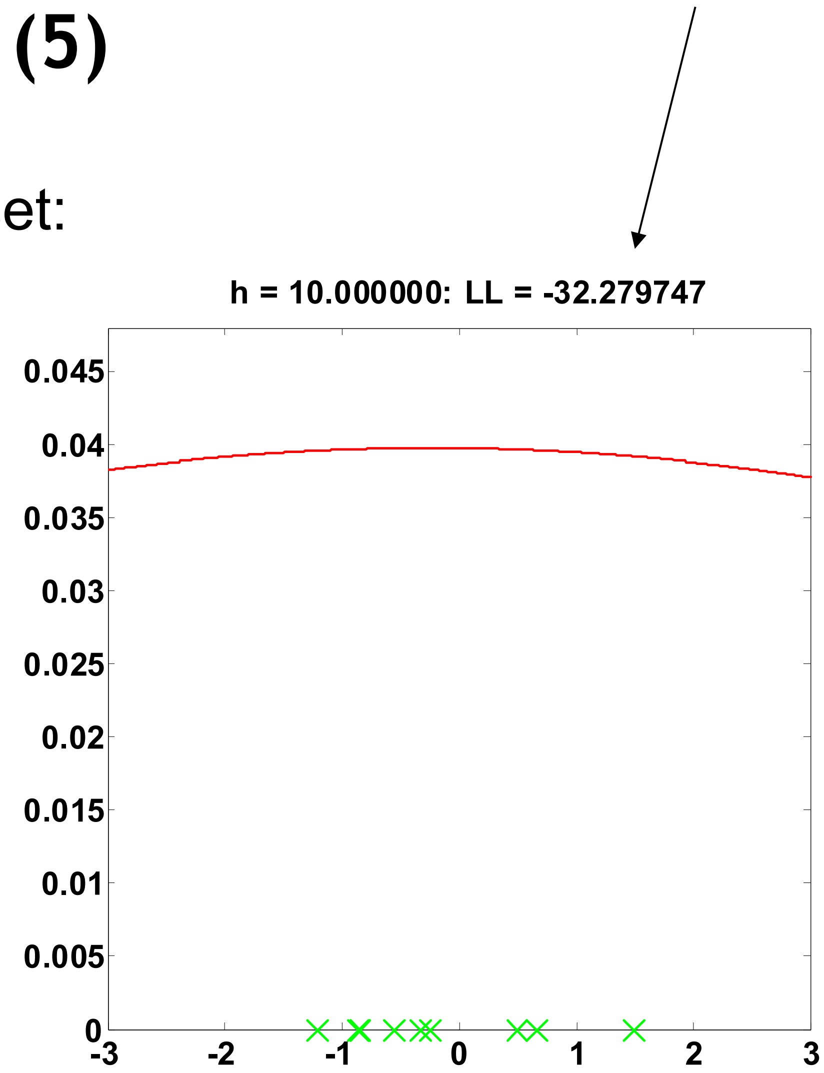
  (this assumes independence!)

  - **Maximize log-likelihood** w.r.t. h *(convenient to avoid multiplication)*:

$$LL = \log(g(\boldsymbol{x}_1, \ldots, \boldsymbol{x}_n)) = \sum_{i=1}^{n} \log(\hat{p}(\boldsymbol{x}_i \mid h))$$

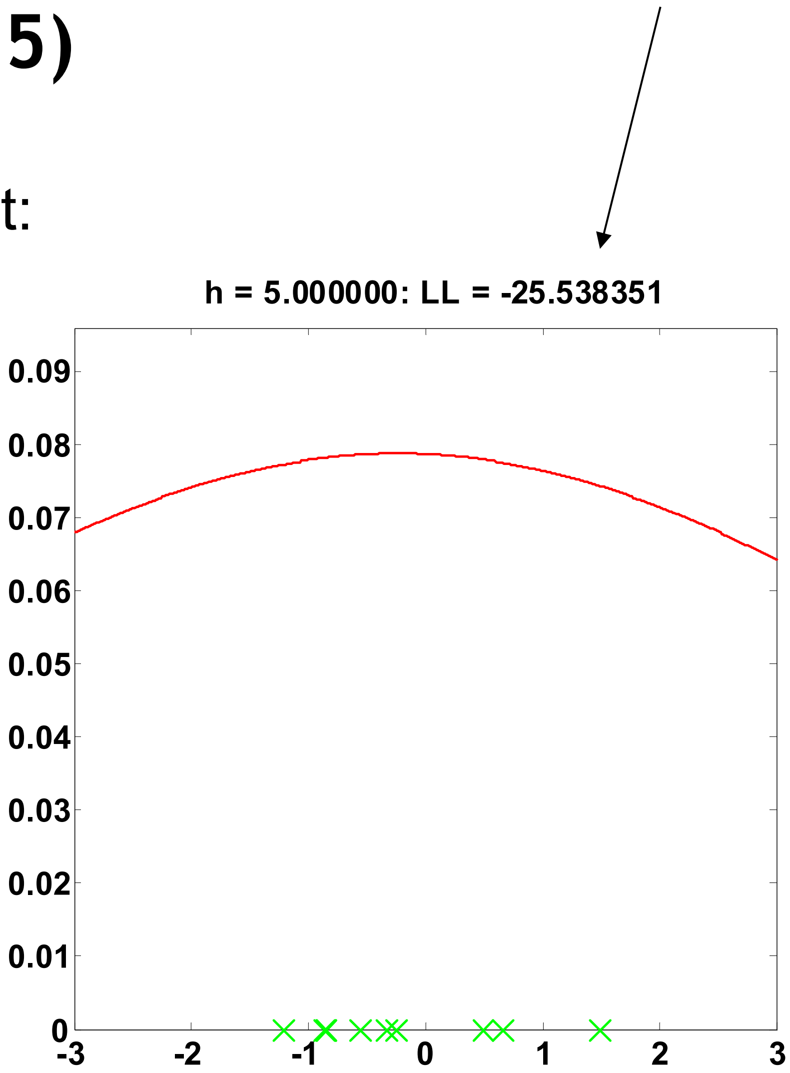
Parzen density estimation (5)

- Maximum likelihood on training set:



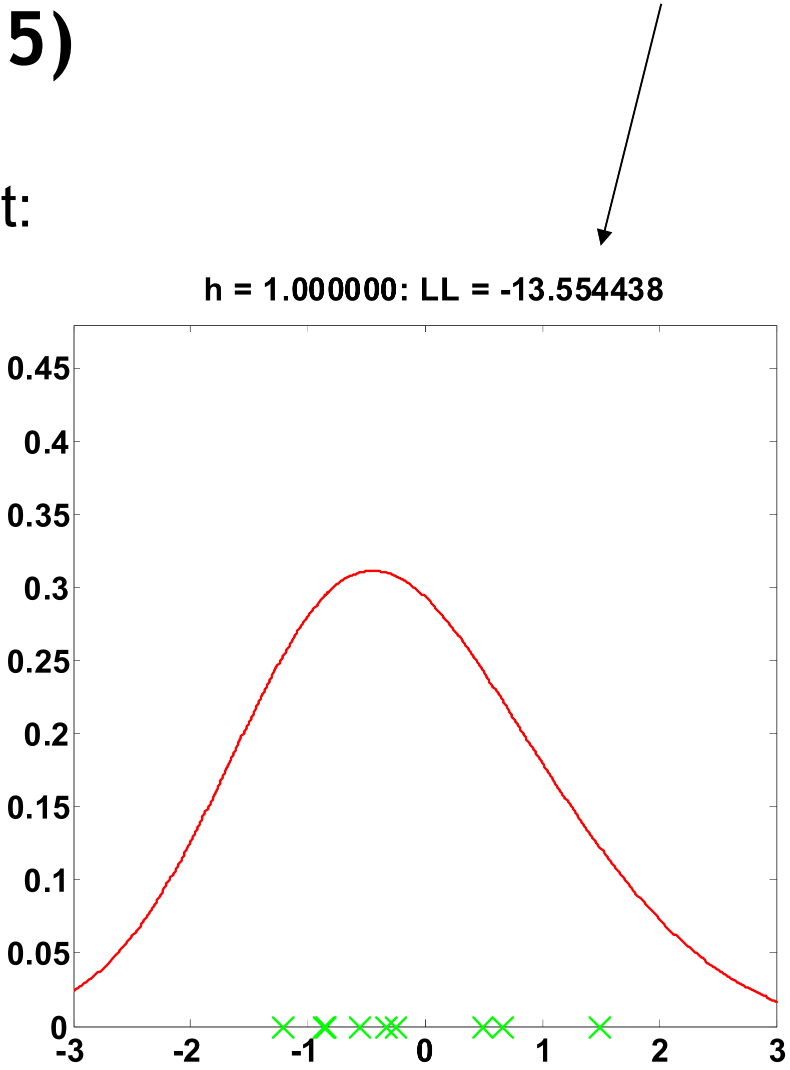
Parzen density estimation (5)

- Maximum likelihood on training set:



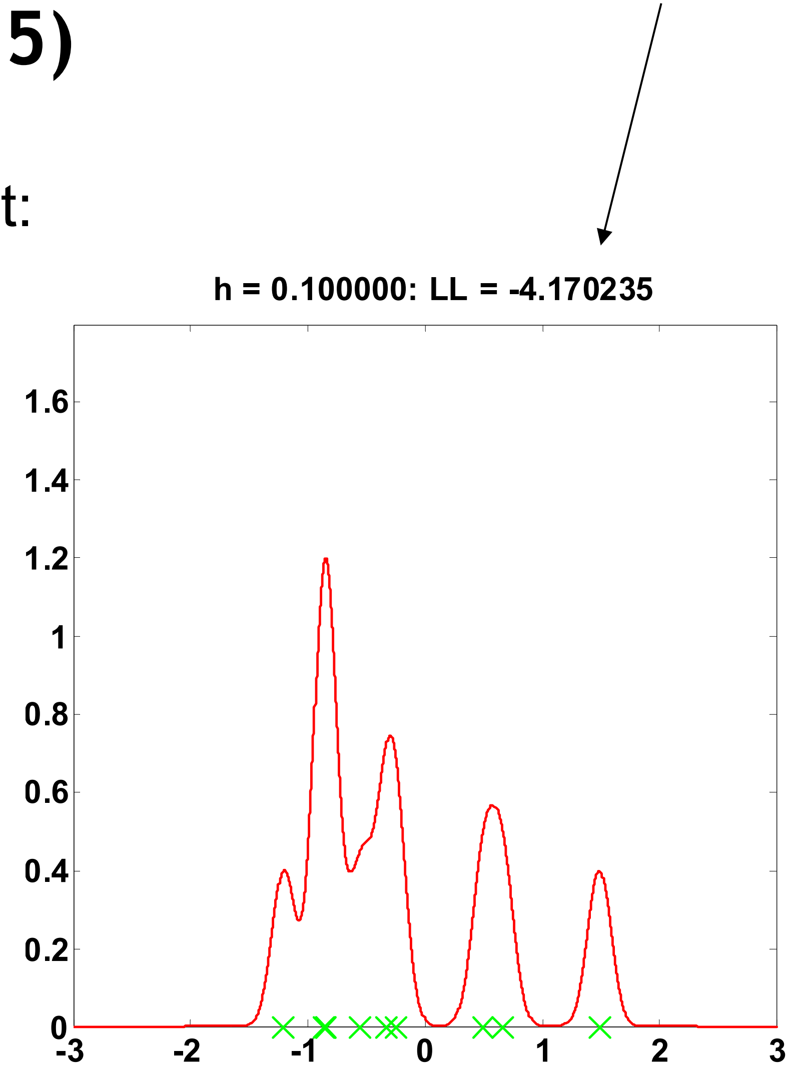
Parzen density estimation (5)

- Maximum likelihood on training set:



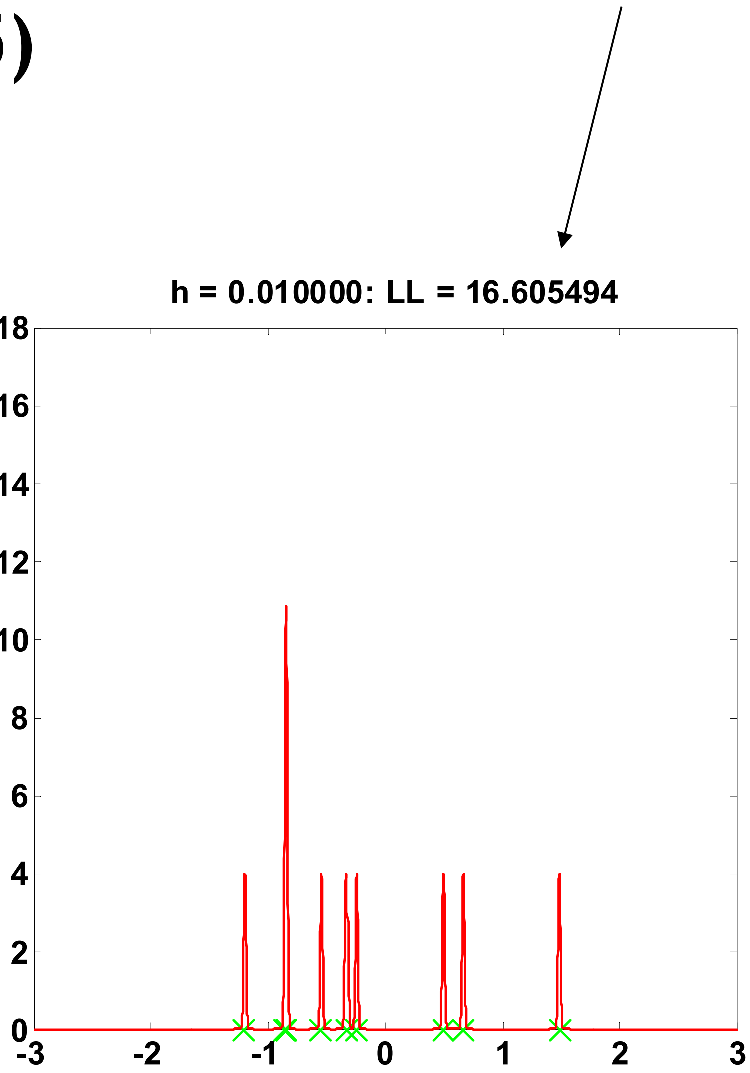
Parzen density estimation (5)

- Maximum likelihood on training set:



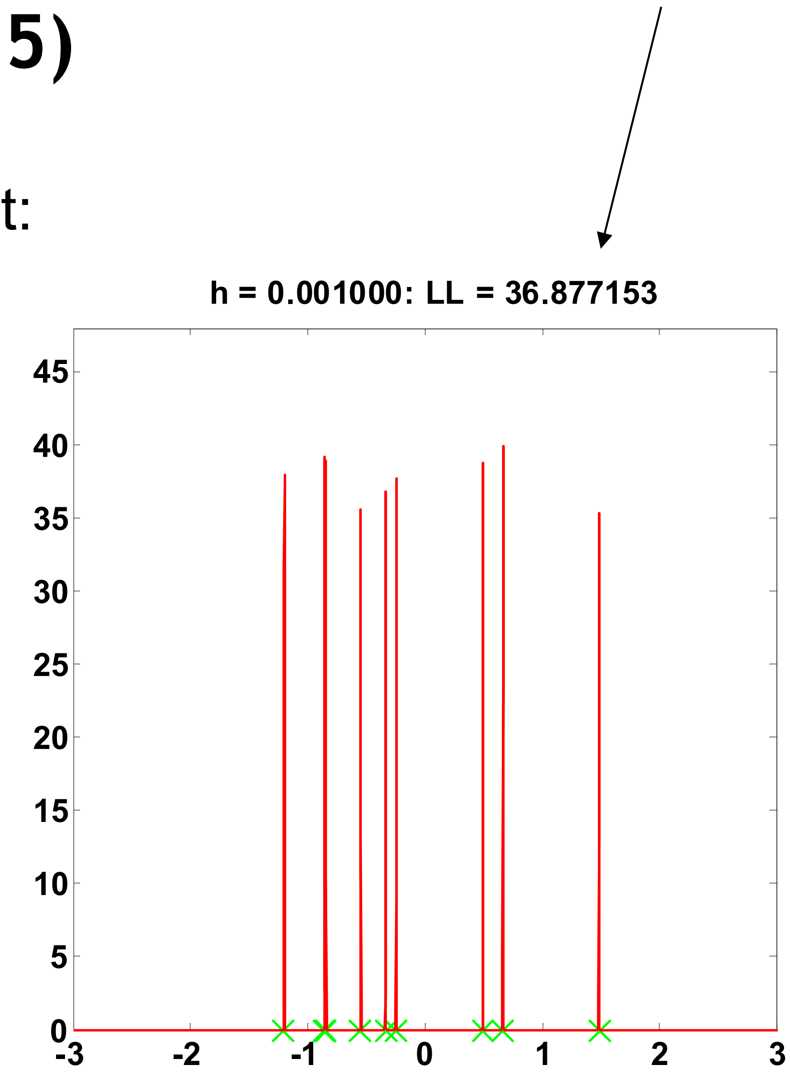
Parzen density estimation (5)

- Maximum likelihood on training set:



Parzen density estimation (5)

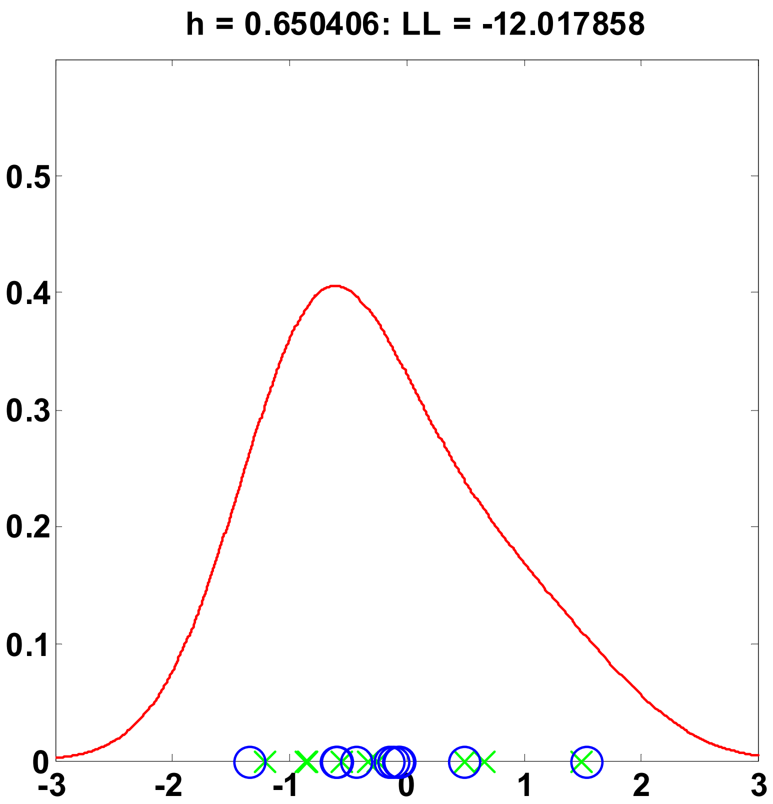
- Maximum likelihood on training set:
  - $h \rightarrow 0$: $LL \rightarrow \infty$
  - **Extreme example of *overtraining* :**
    fitting data too much



Cross-validation

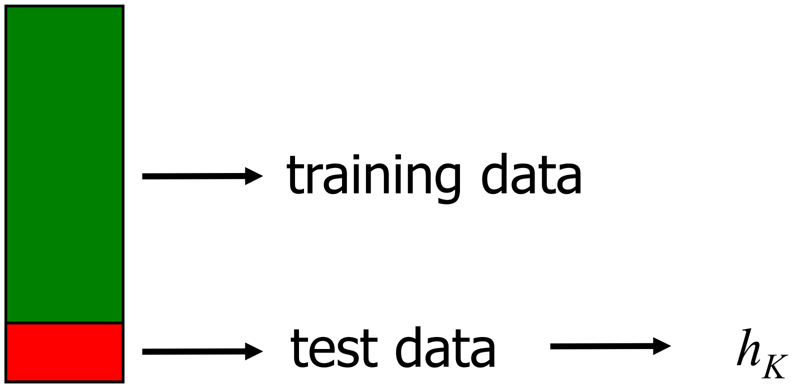
- Solution:
    - Split data into *training set* and *validation set*
    - Optimise h w.r.t. likelihood of validation set, given Parzen model trained on training set

- Problems:
    - Uses a lot of valuable data
    - Sensitive to split of data



Cross-validation (2)

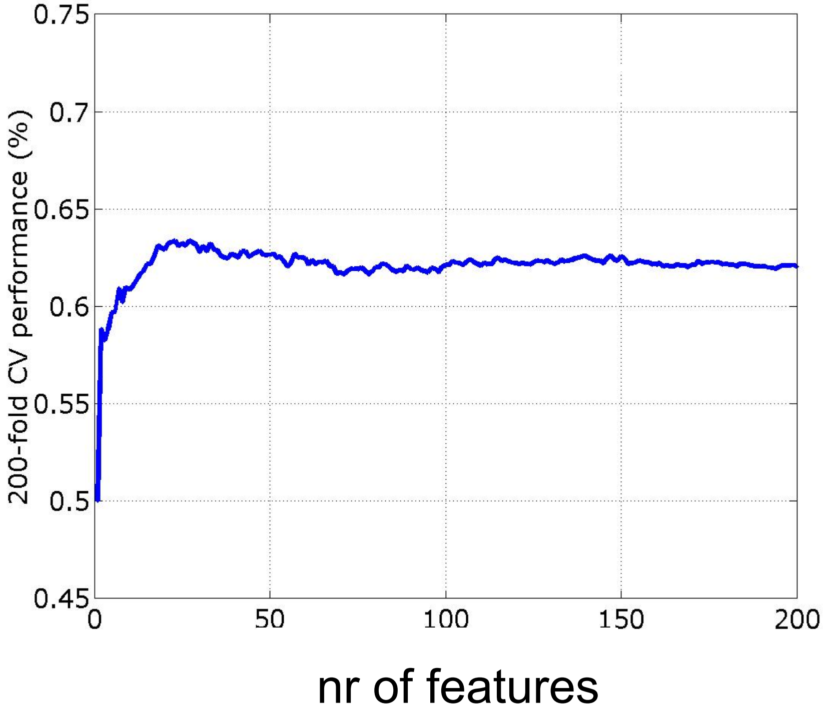
- Better solution: *K*-fold crossvalidation
  - Split data into K parts ($K = n$: leave-one-out)
  - Repeat K times:
    - Find h using $(K - 1)$ parts for training and 1 part for testing
  - Use average of h's as kernel width

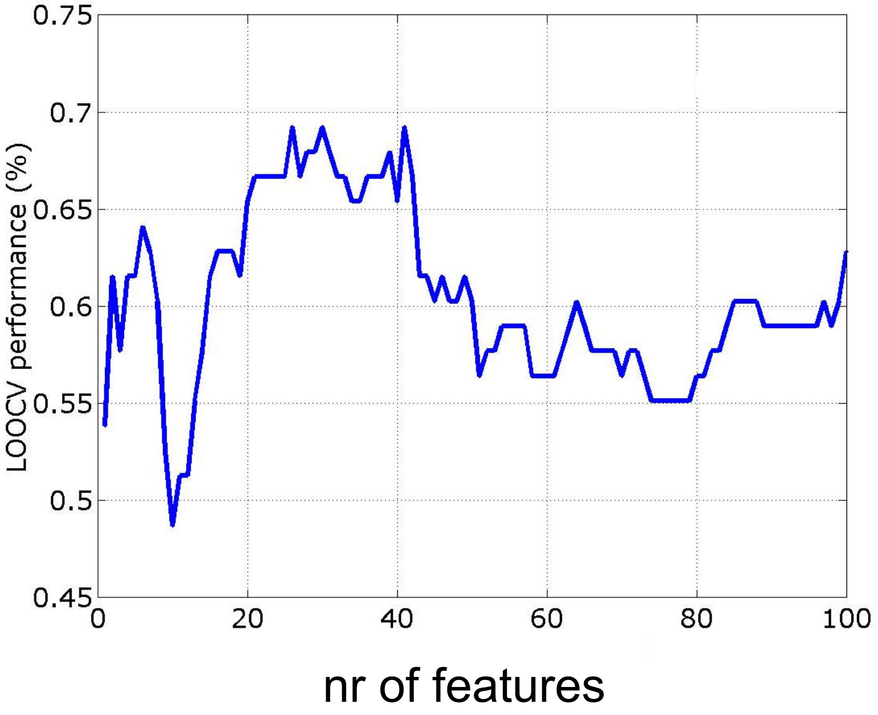


(will return)

Cross-validation (3)

- (Prefer) *K*-fold cross-validation over leave-one-out
  - Smoother (less variance) and more biased (conservative)





Bootstrap

- Alternative to cross-validation:
  - Repeat K times:
    - Draw n objects from the dataset, **with replacement** (some objects will be selected more than once)
    - Test using objects that were not selected

- Cross-validation and bootstrap estimates are *biased*
  - They are conservative (i.e. too pessimistic) because they do not use all data available

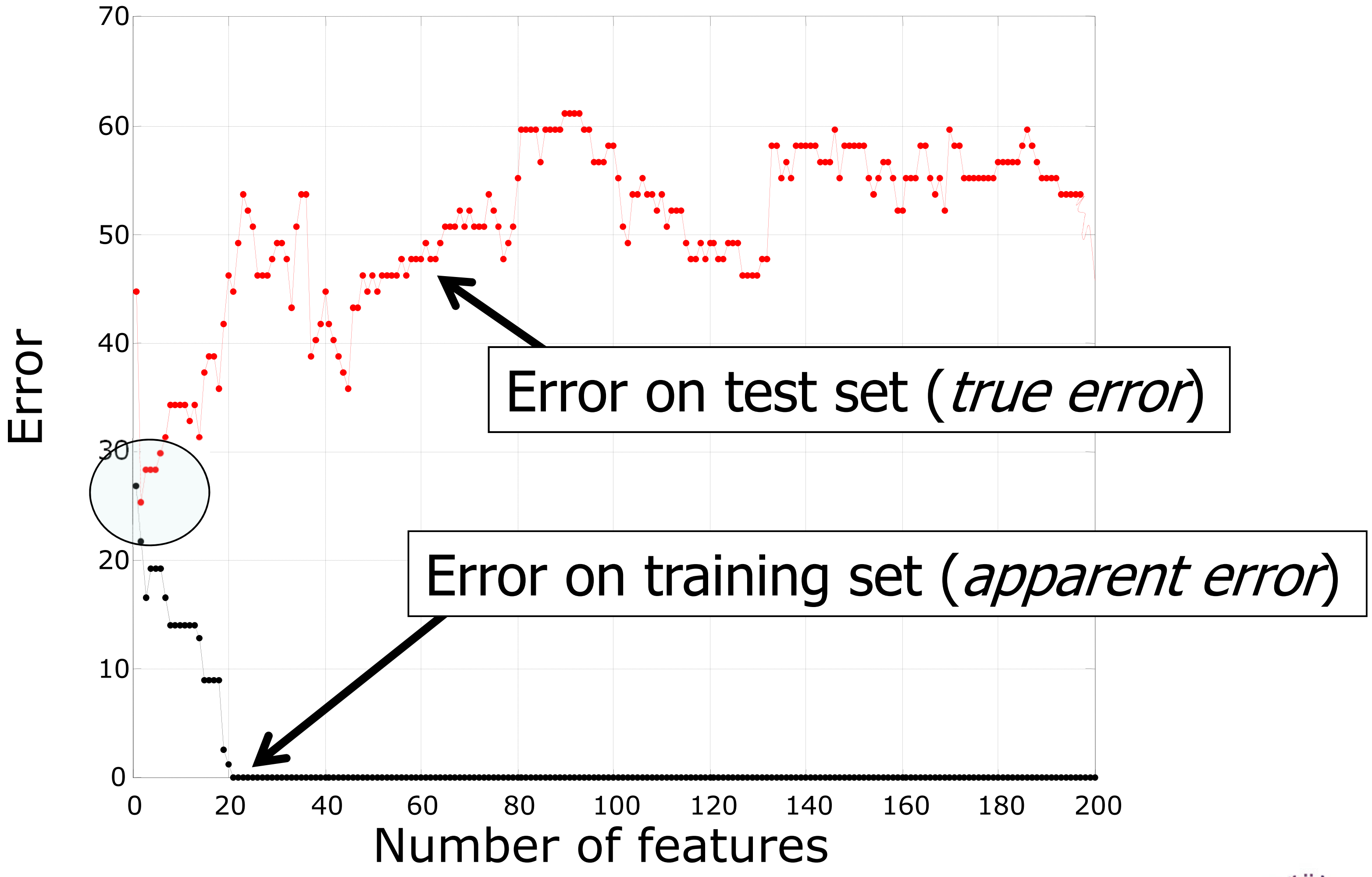
You want to get an estimate when you fit on complete/all data.
CV/Bootstrap are thus biased wrt fitting on complete data!

Training, test and validation sets

- Terminology:
  - A *training set* is used to estimate parameters
  - An optional *validation set* is used to optimize parameter settings, e.g. by calculating classifier error on this set
  - **A *test set* is only used to judge performance of the entire classifier (only used once!)**

- Error estimates:
  - On training set: *apparent error*
  - On test set: *true error*

Training, test and validation sets (2)

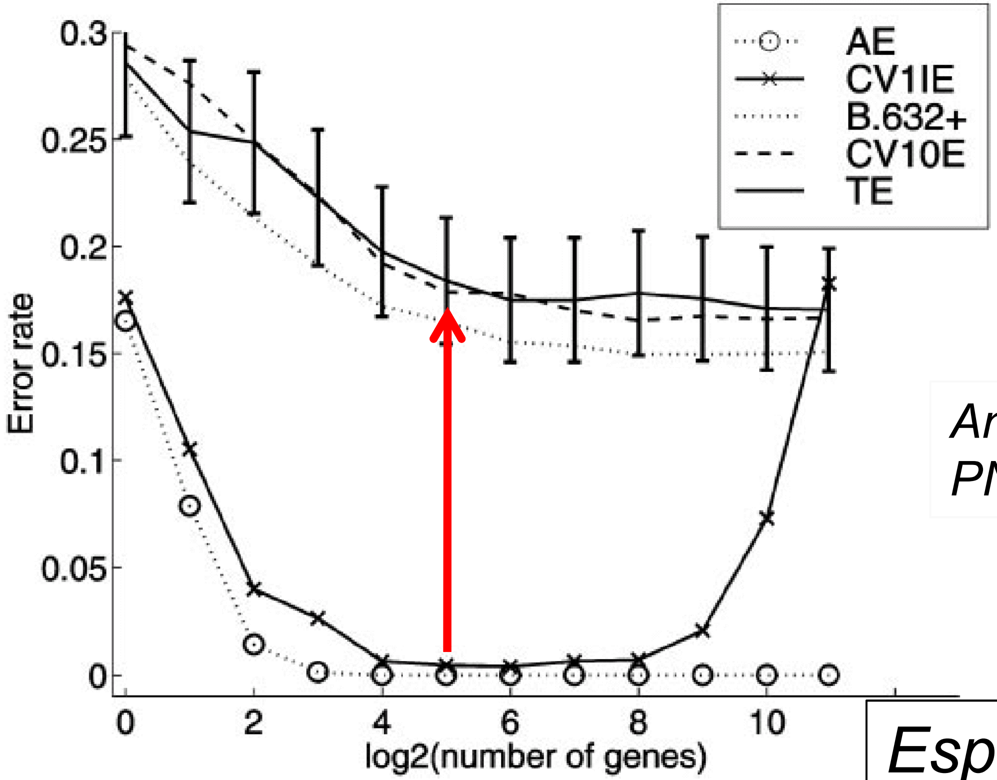


Error on test set (*true error*)

Error on training set (*apparent error*)

Training, test and validation sets (3)

- The test set should *never* be used to set any parameters! This leads to biased estimates of performance -- in practice we may do much worse than we predict



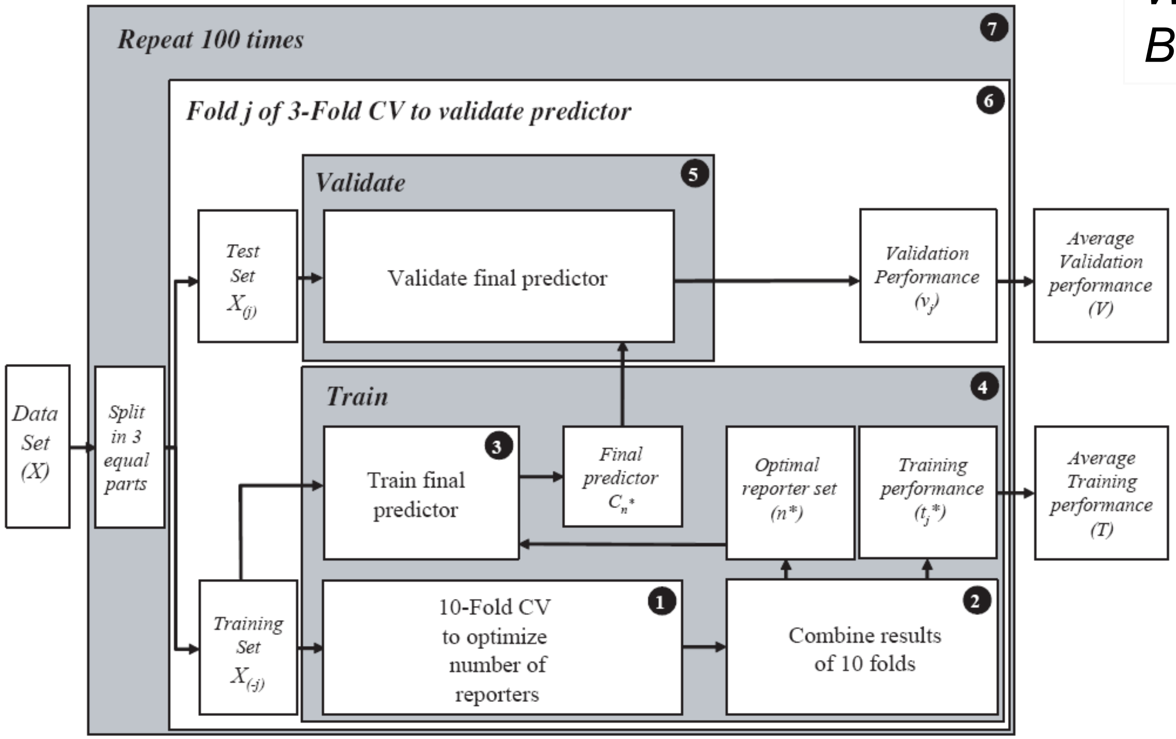
Ambroise et al., PNAS 2002

Especially in bioinformatics i.e. p>>n problems

Training, test and validation sets (4)

- Can lead to complicated schemes for estimating parameters, e.g. double/nested cross-validation loops

Wessels et al., Bioinformatics 2005



Recapitulation

- *Bayesian estimation*
  - provides a framework for minimizing cost due to errors
  - combines class-conditional and prior distributions into posterior ones
- We never *know* these distributions, so we have to *estimate* them; this is problematic due to the *curse of dimensionality*
- Possible approaches:
  - *Parametric*: e.g. Gaussian
  - *Nonparametric:* histogramming, *k*-nearest neighbor density estimation, Parzen density estimation

Recapitulation (2)

- *Maximum likelihood estimation* is a method for estimating parameters of density functions
- To optimize parameters, the error should be calculated on a *validation set*
- A completely independent *test set* should only be used to judge performance of the final classifier
- *Cross-validation* and *bootstrapping* can help to estimate performance when little data is available