



Machine Learning for Bioinformatics & Systems Biology

1. Introduction & density estimation

Marcel Reinders *Delft University of Technology*

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 11/10	Marcel Reinders	Introduction to machine learning Bayesian framework Density estimation Bayesian classification
Tuesday 12/10	Perry Moerland	Parametric classifiers Nonparametric classifiers Discriminant analysis Decision trees & random forests
Wednesday 13/10	Lodewyk Wessels	Feature selection Sparse classifiers Feature extraction Embeddings
Thursday 14/10	Perry Moerland	Hierarchical clustering Agglomerative clustering Model-based clustering Hidden Markov models
Friday 15/10	Marcel Reinders	Artificial neural networks Support vector machines Classifier ensembles Complexity

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 **November 5, 2021 (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: 15-16 February 2022, Lunteren
- Courses:

Upcoming courses

Date	Level	Course	Duration
11-15 Oct 2021	fund.	Machine Learning	5 days
18-22 Oct 2021	other	Single Cell Analysis	5 days
13-17 Dec 2021	fund.	Integrated modeling and optimization	5 days

- 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

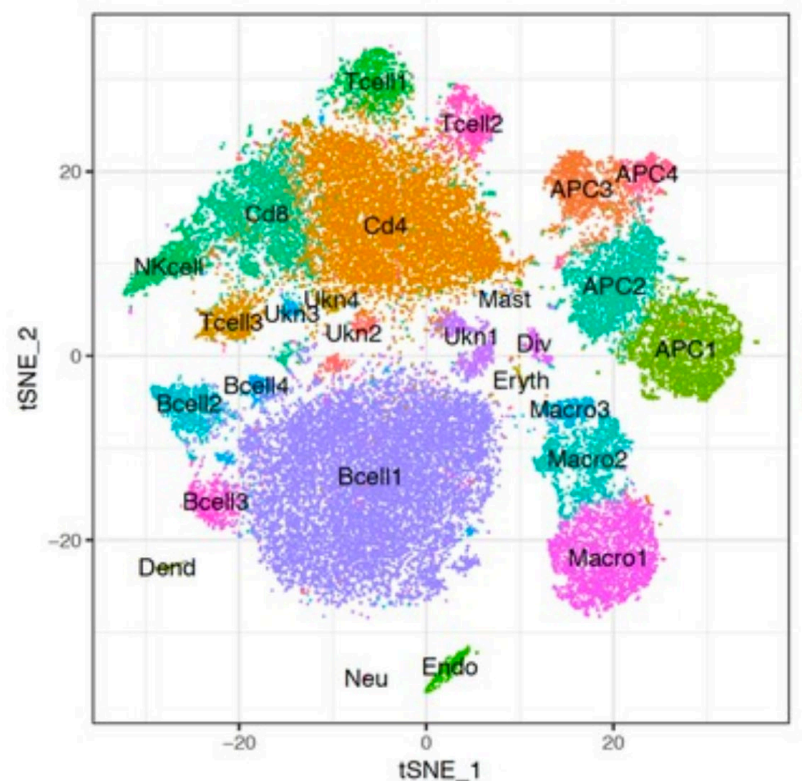


Machine learning (3)

- 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

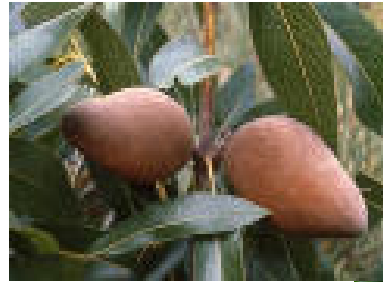
- After having followed this course, the student has a good understanding of **a wide range of machine learning techniques** and is able to **recognize what method is most applicable** to data analysis problems (s)he encounters in bioinformatics and systems biology applications.
- Many problems are in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

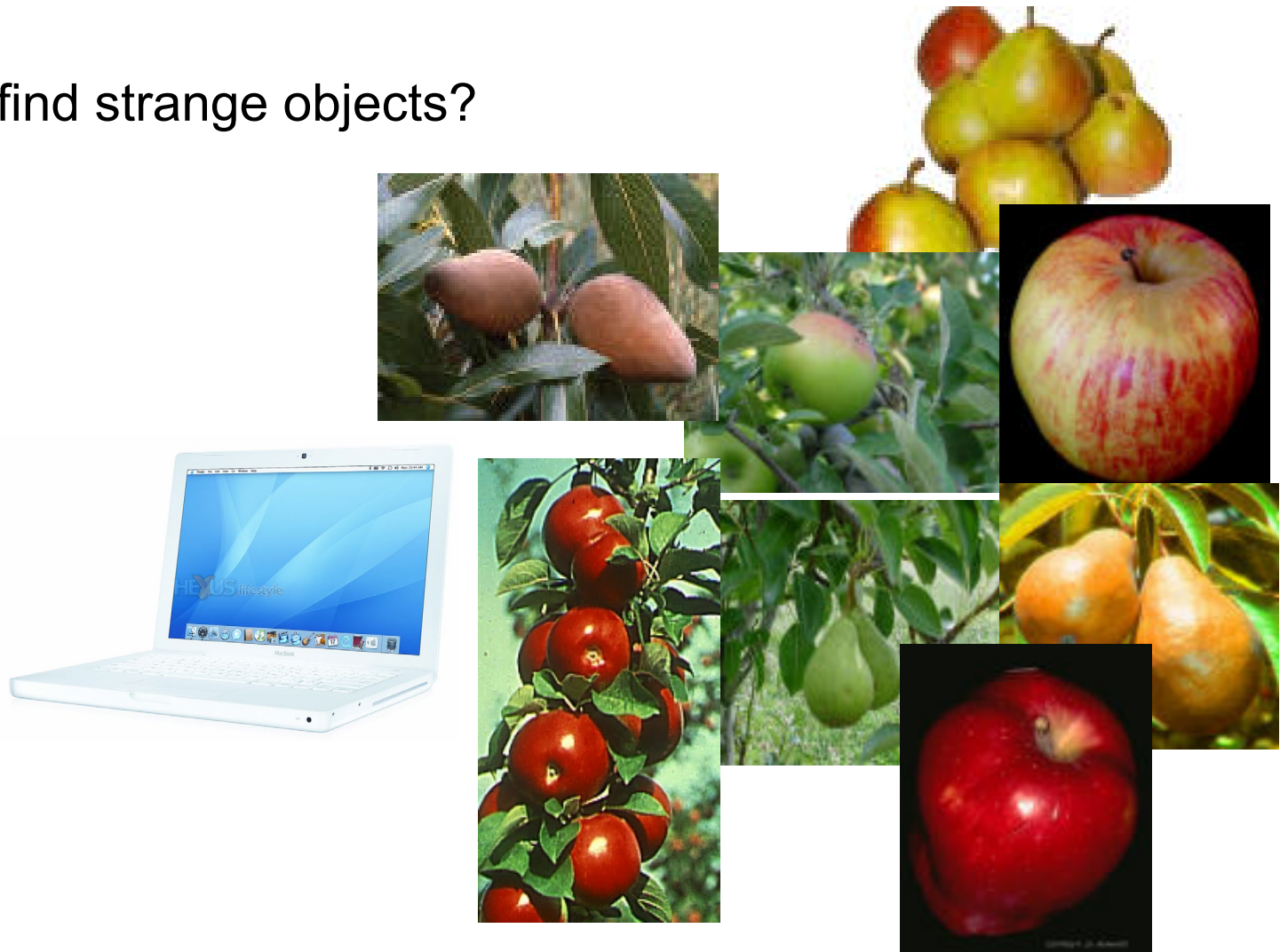
Clustering

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



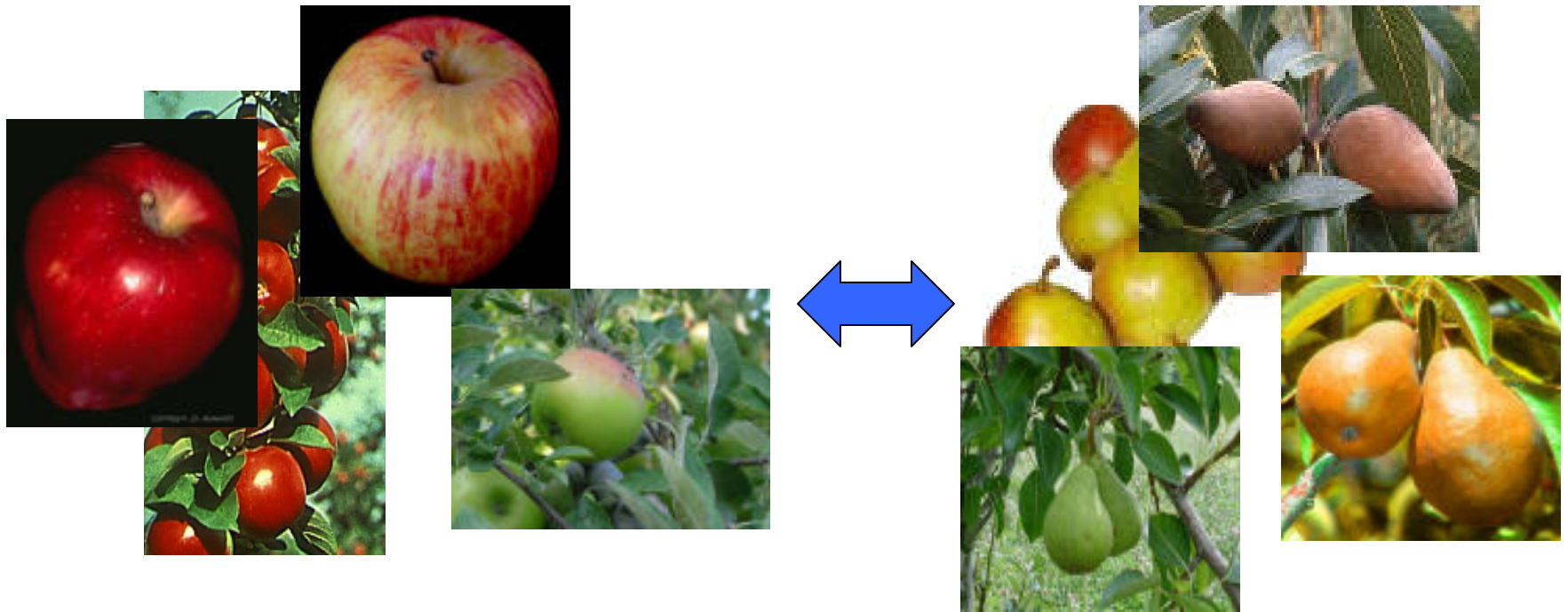
Outlier detection

- Can we find strange objects?



Dimensionality reduction

- Can we find predictive measurements?



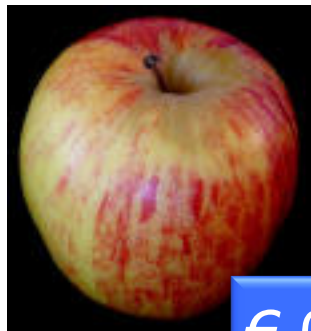
Red



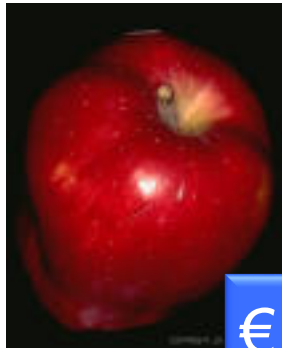
Yellow

Regression

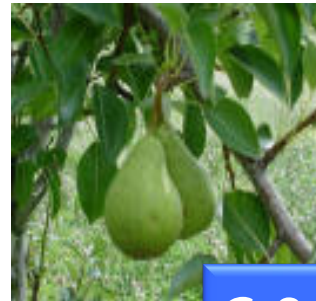
- Can we predict real-valued outputs?



€ 0.25



€ 0.30



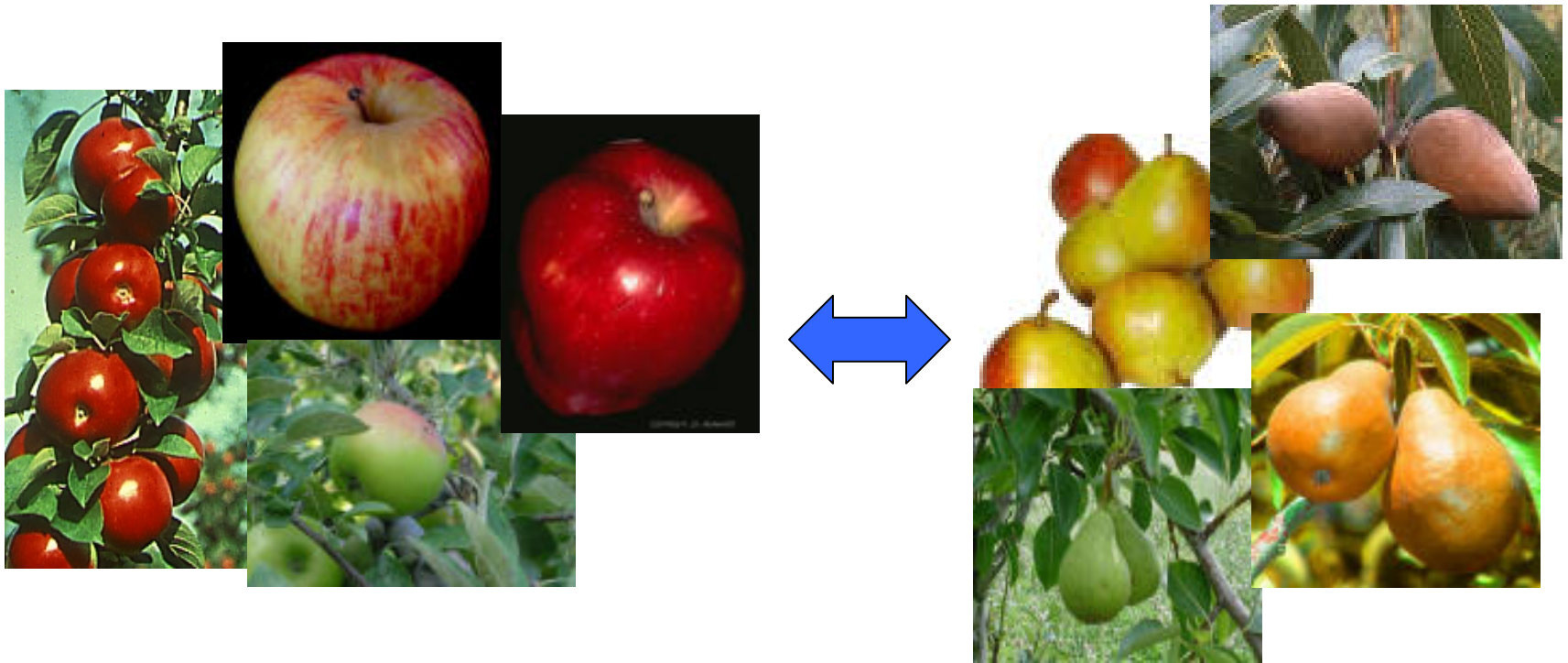
€ 0.40



€ 0.45

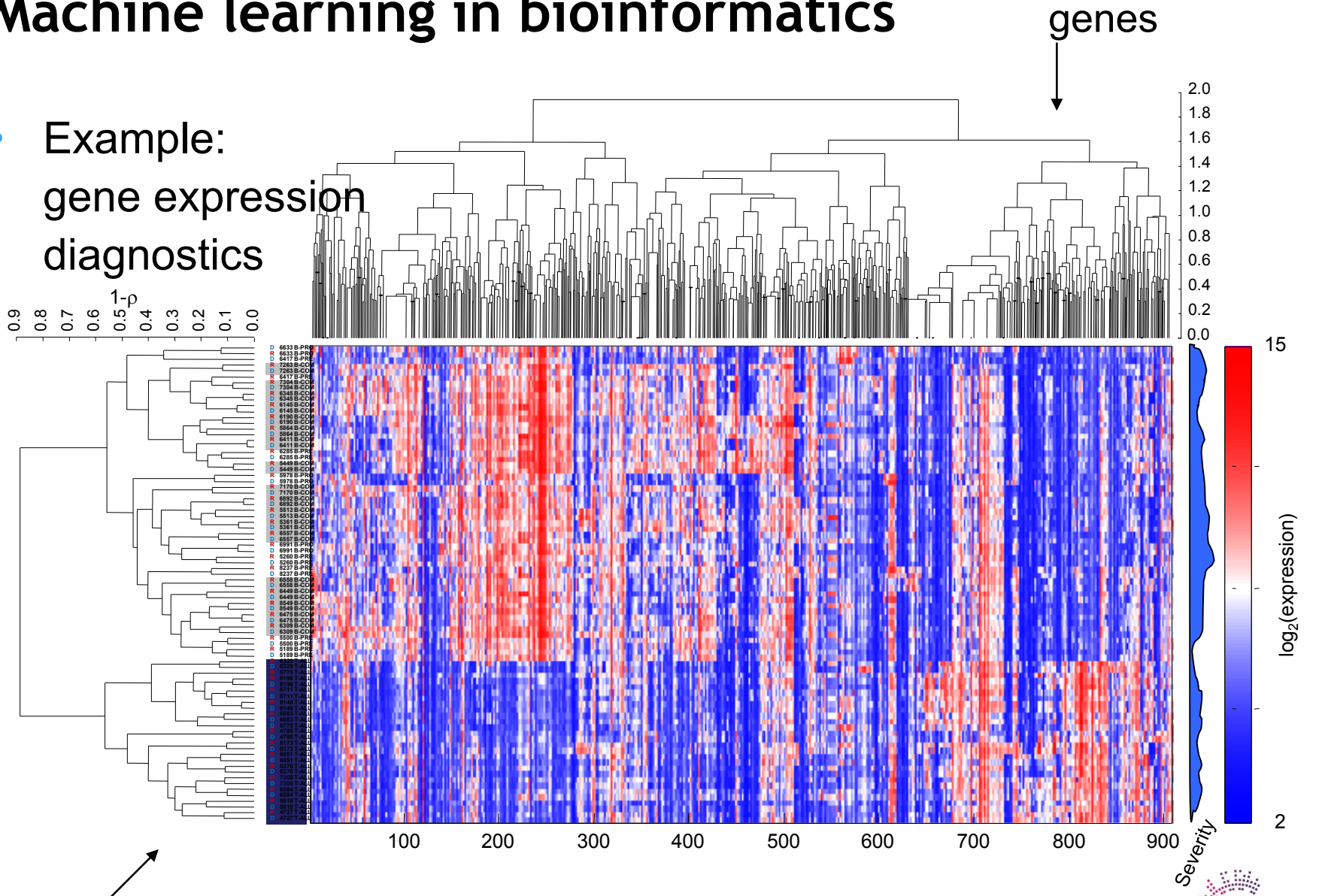
Classification

- Can we distinguish apples from pears?



Machine learning in bioinformatics

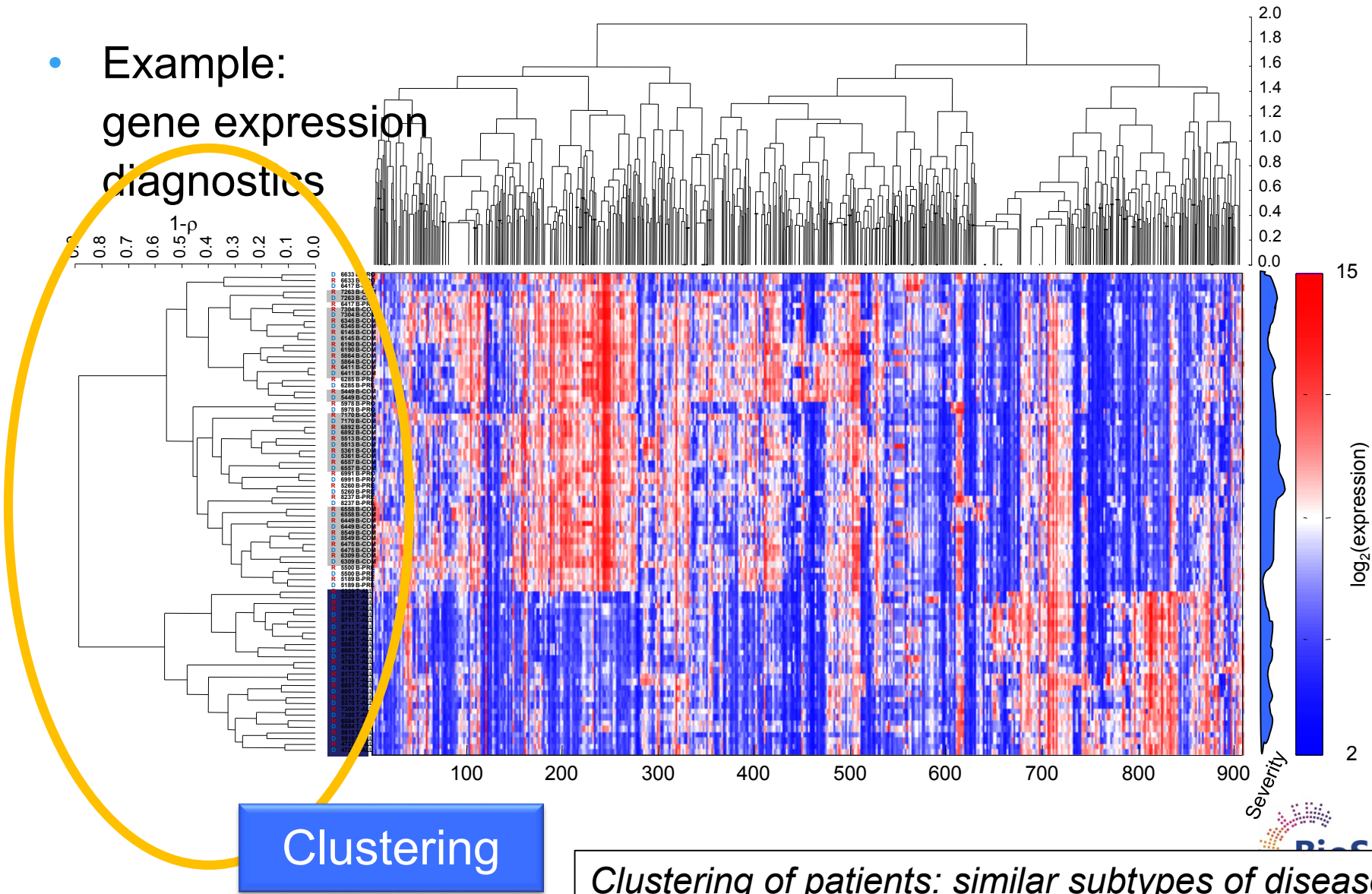
- Example: gene expression diagnostics



diagnosis/relapse in childhood leukemia

Machine learning in bioinformatics

- Example:
gene expression
diagnostics



Clustering

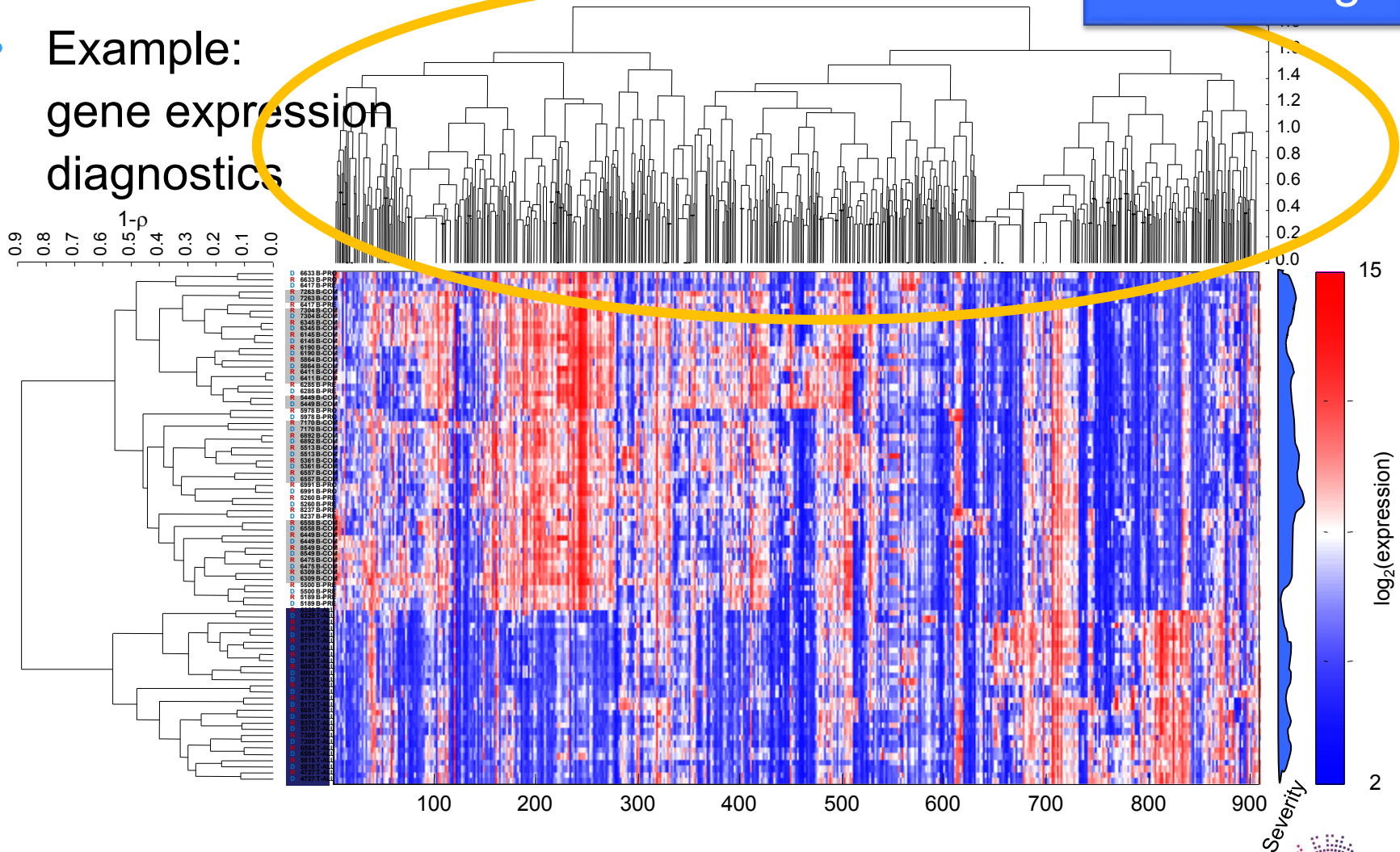
Clustering of patients: similar subtypes of disease



Machine learning in bioinformatics

Clustering

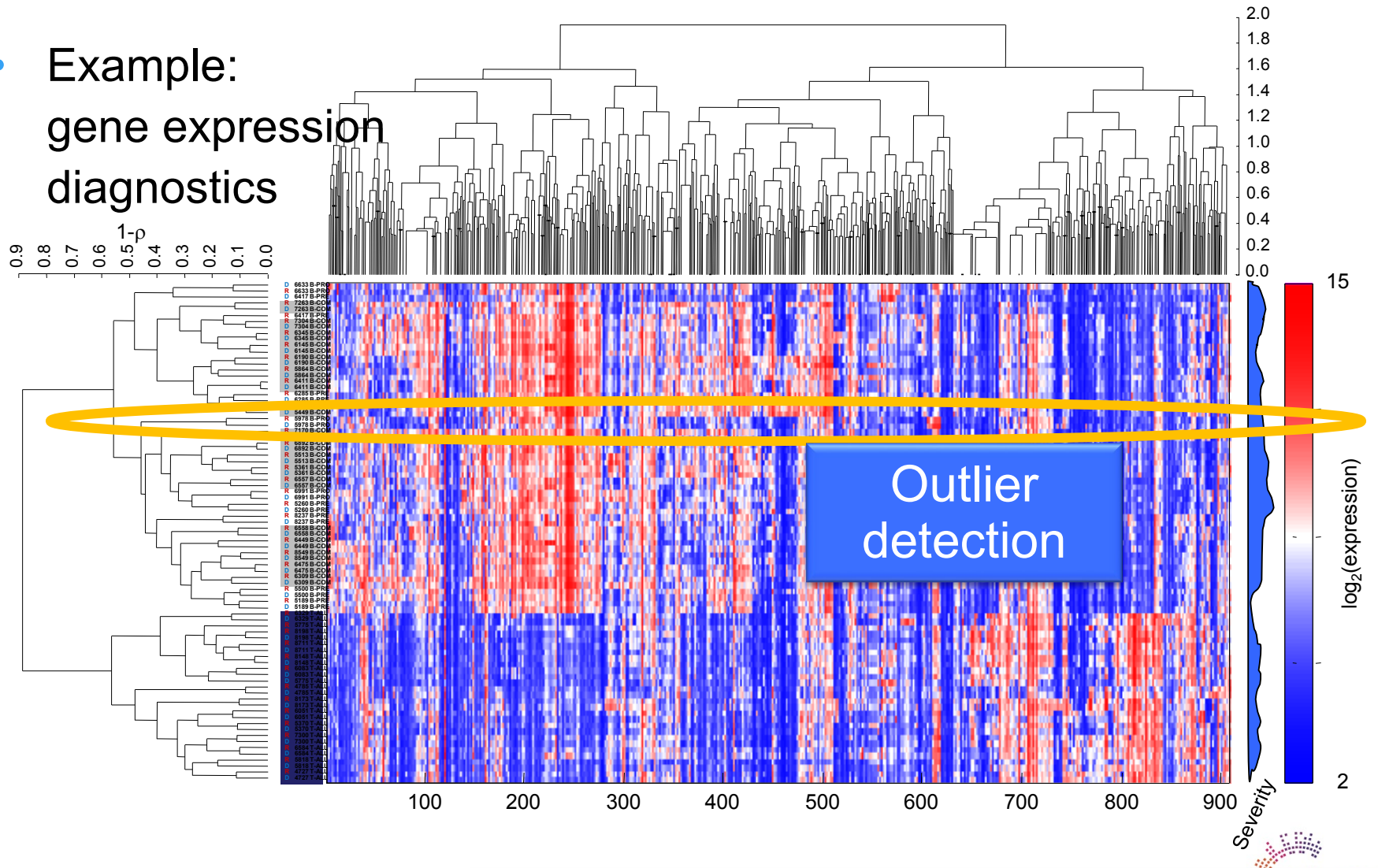
- Example: gene expression diagnostics



Clustering of genes: similar 'disruptive' processes

Machine learning in bioinformatics

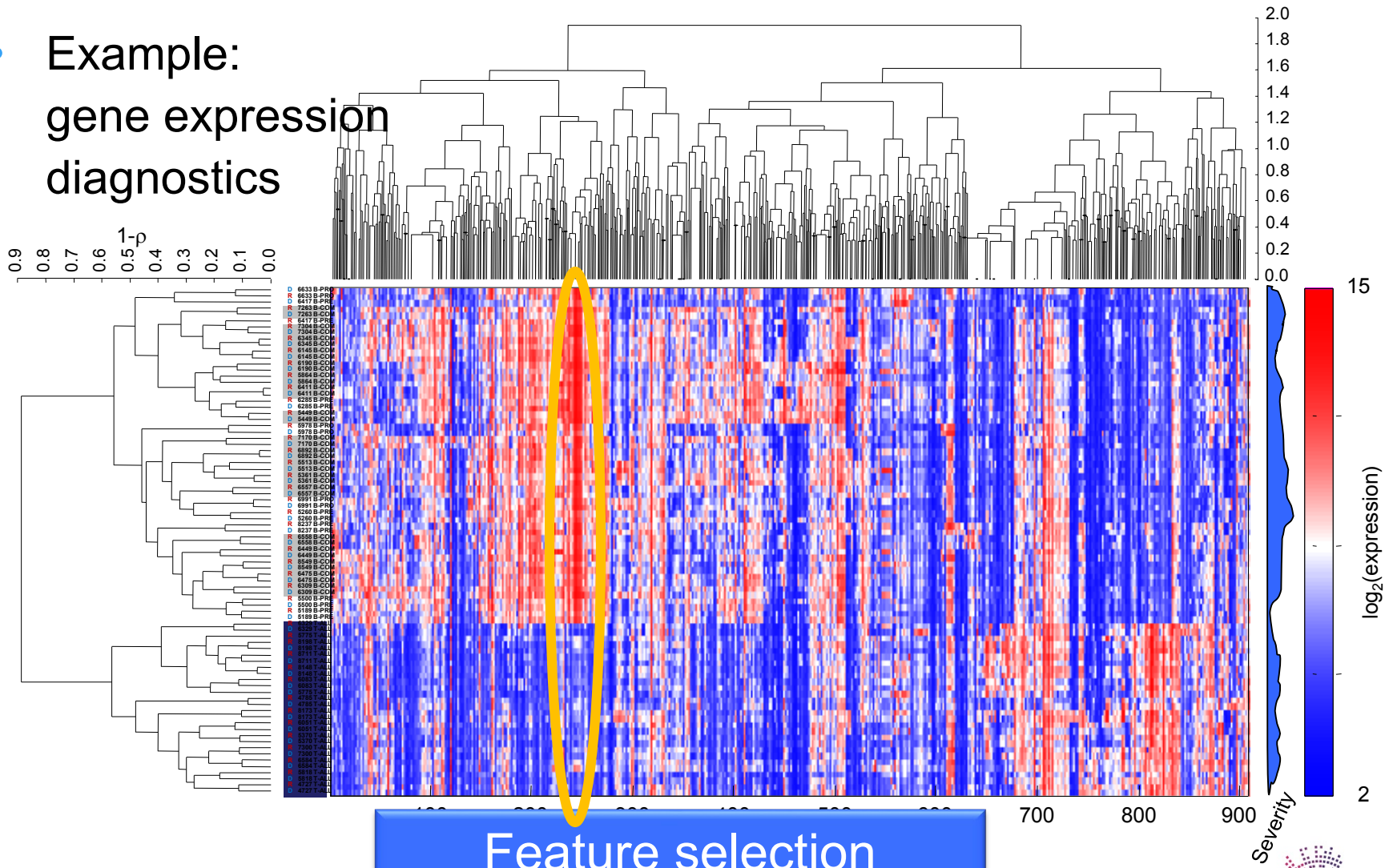
- Example:
gene expression
diagnostics



Technical error / rare patient-rare genetic background

Machine learning in bioinformatics

- Example:
gene expression
diagnostics



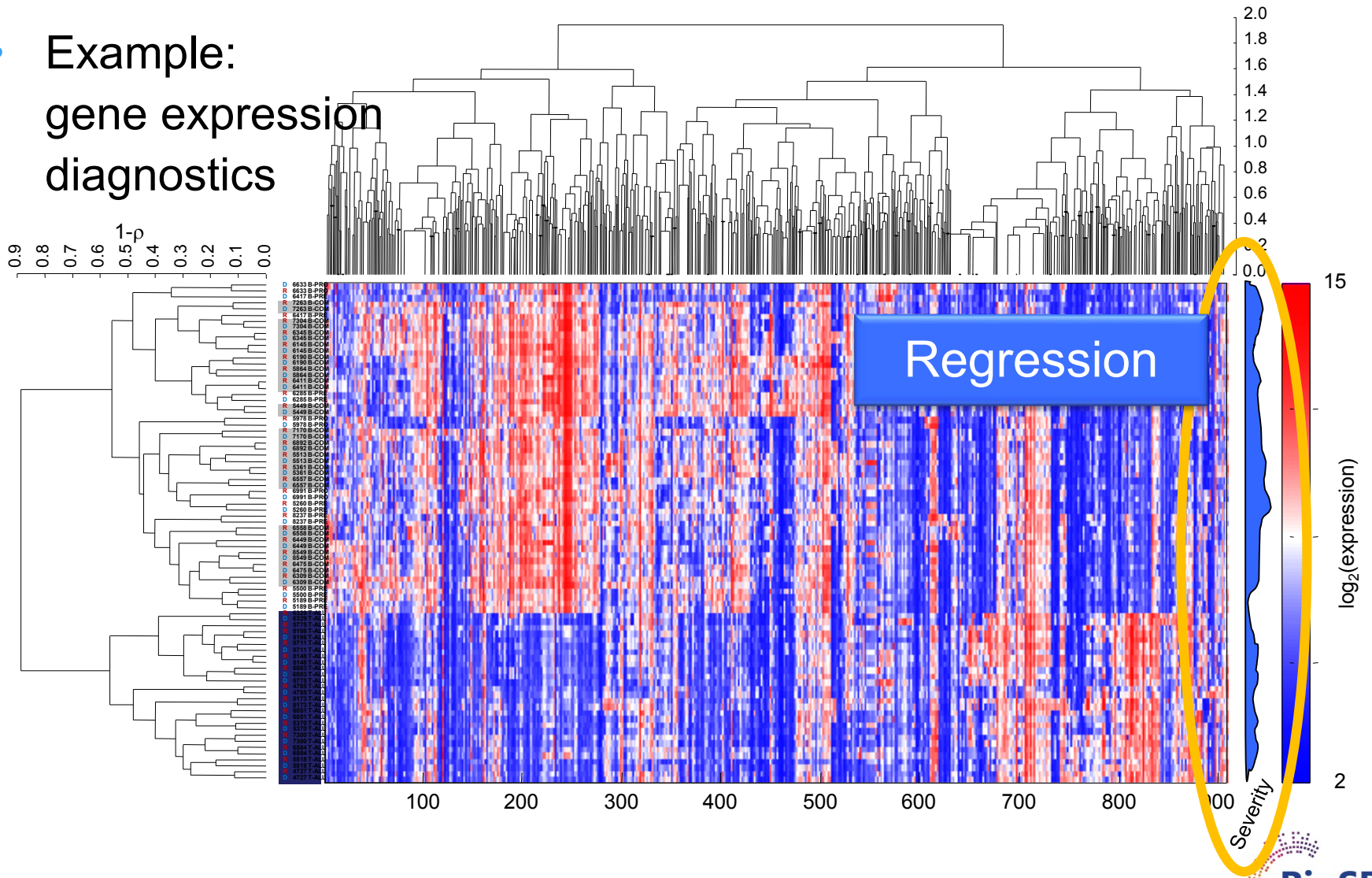
Feature selection
(dimensionality reduction)

Potential biomarkers



Machine learning in bioinformatics

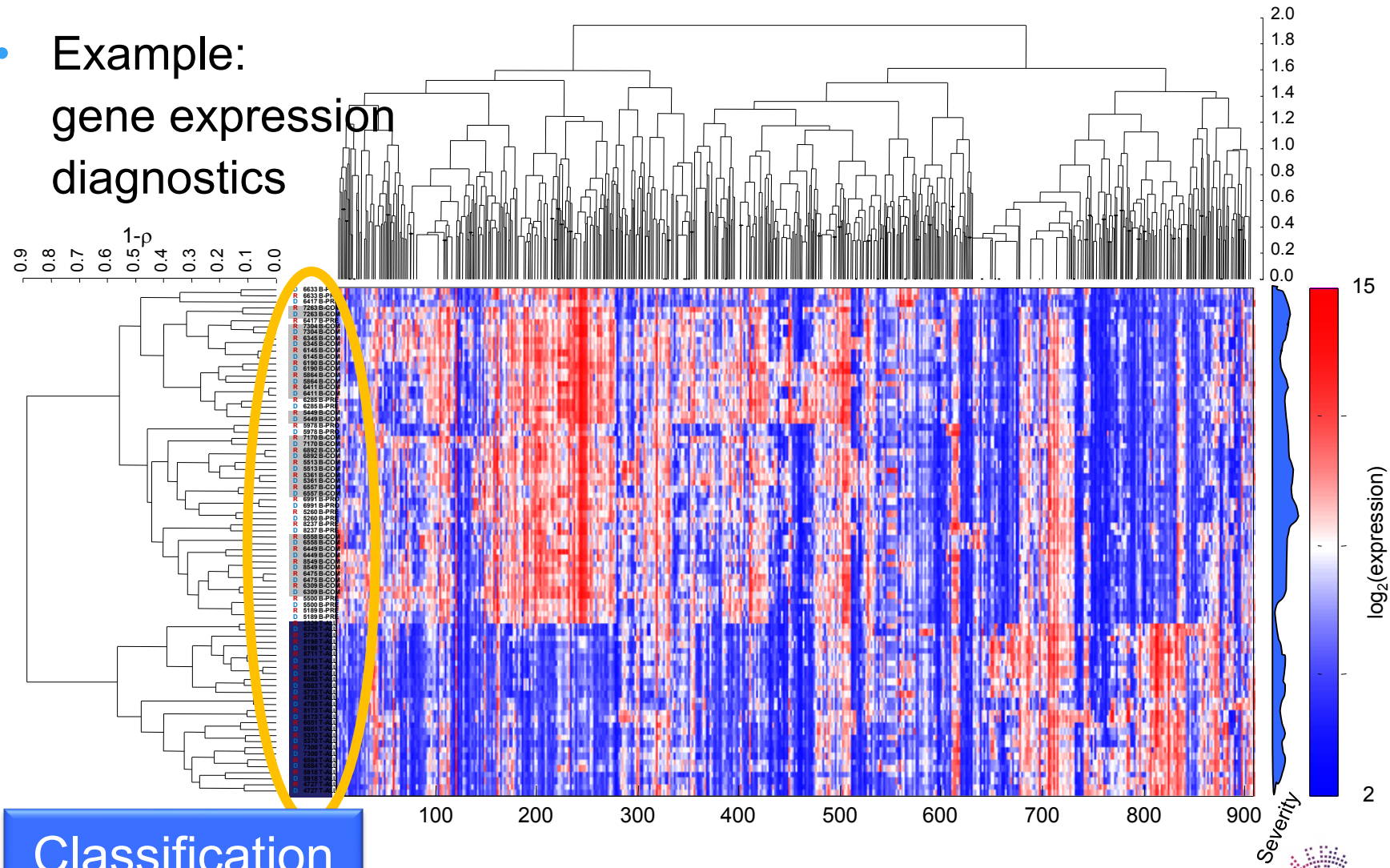
- Example:
gene expression
diagnostics



E.g. Predicting survival time

Machine learning in bioinformatics

- Example:
gene expression
diagnostics



Classification

E.g. Predicting metastasis



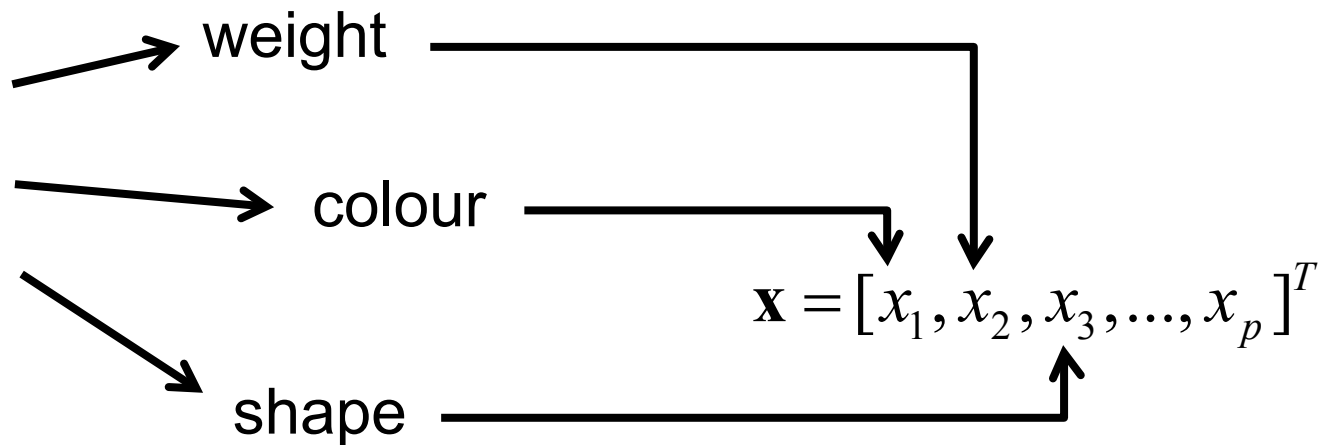
Machine learning in bioinformatics (2)

- 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*



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

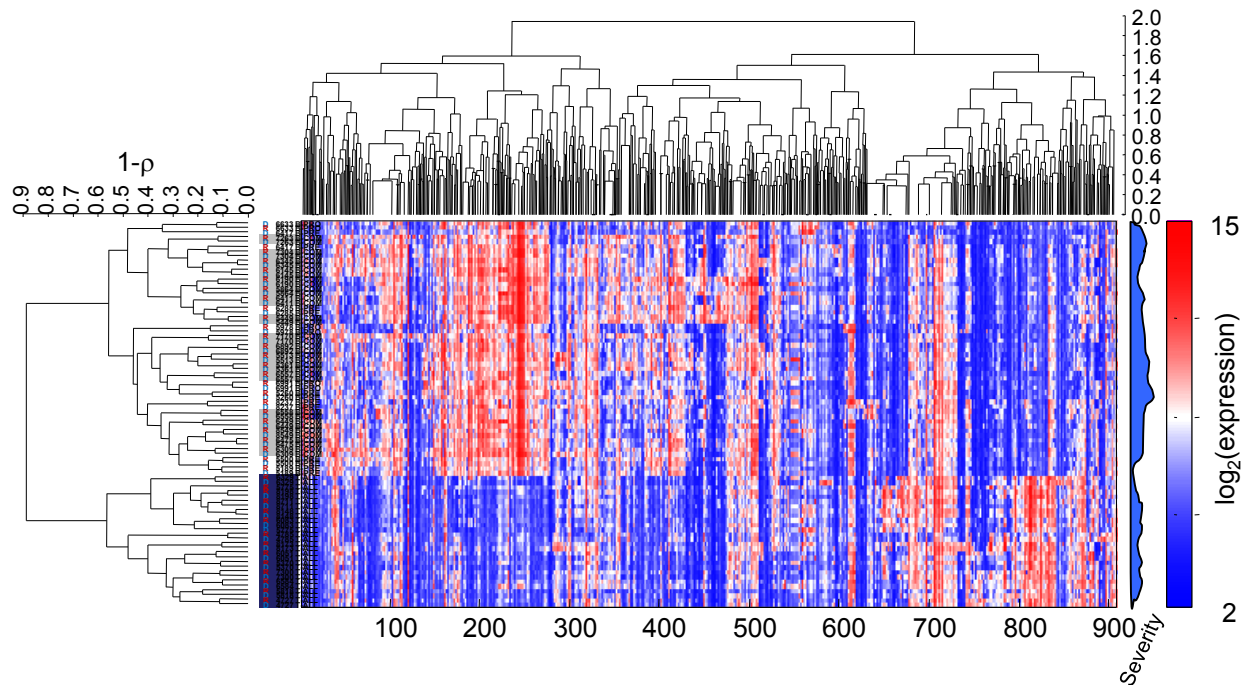
measurement **feature** **labels**

object

dataset

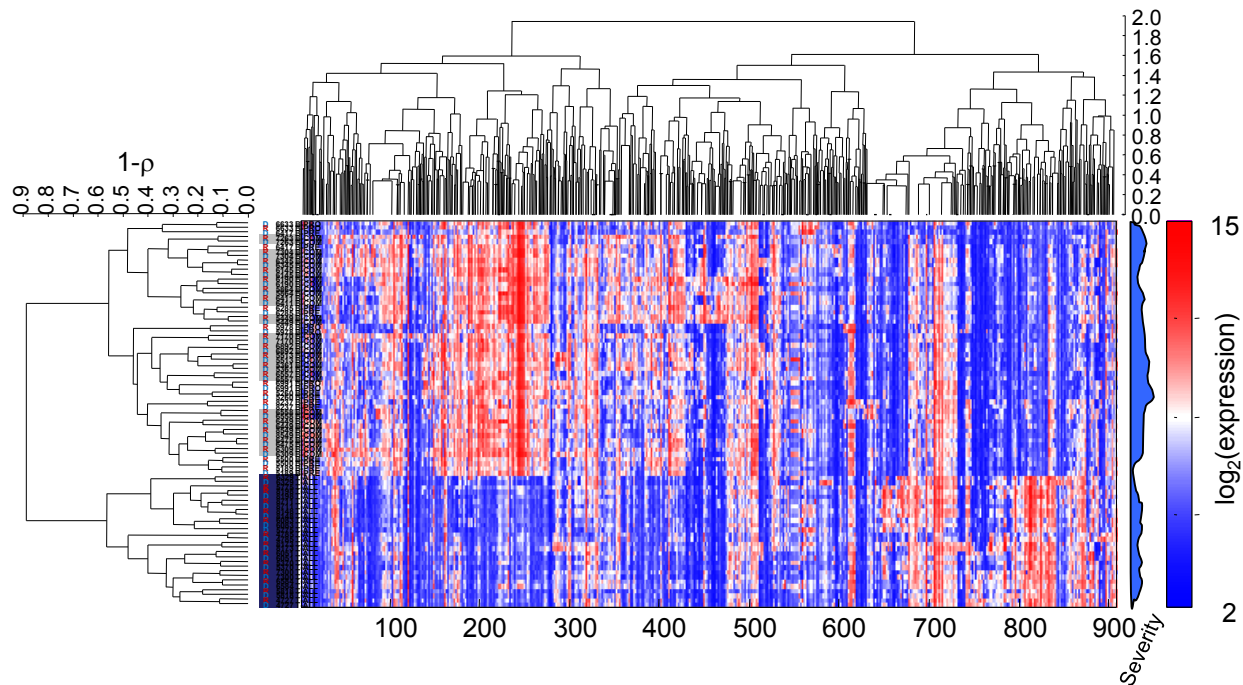
Datasets (2)

- 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



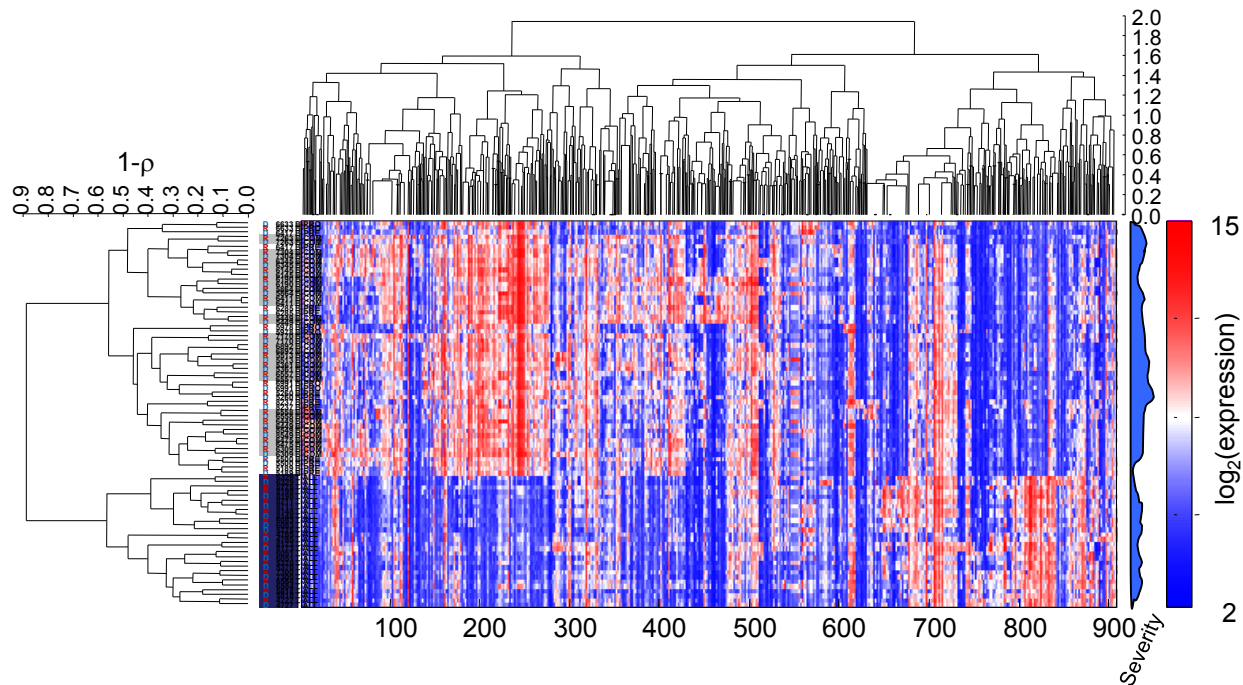
Datasets (2)

- 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



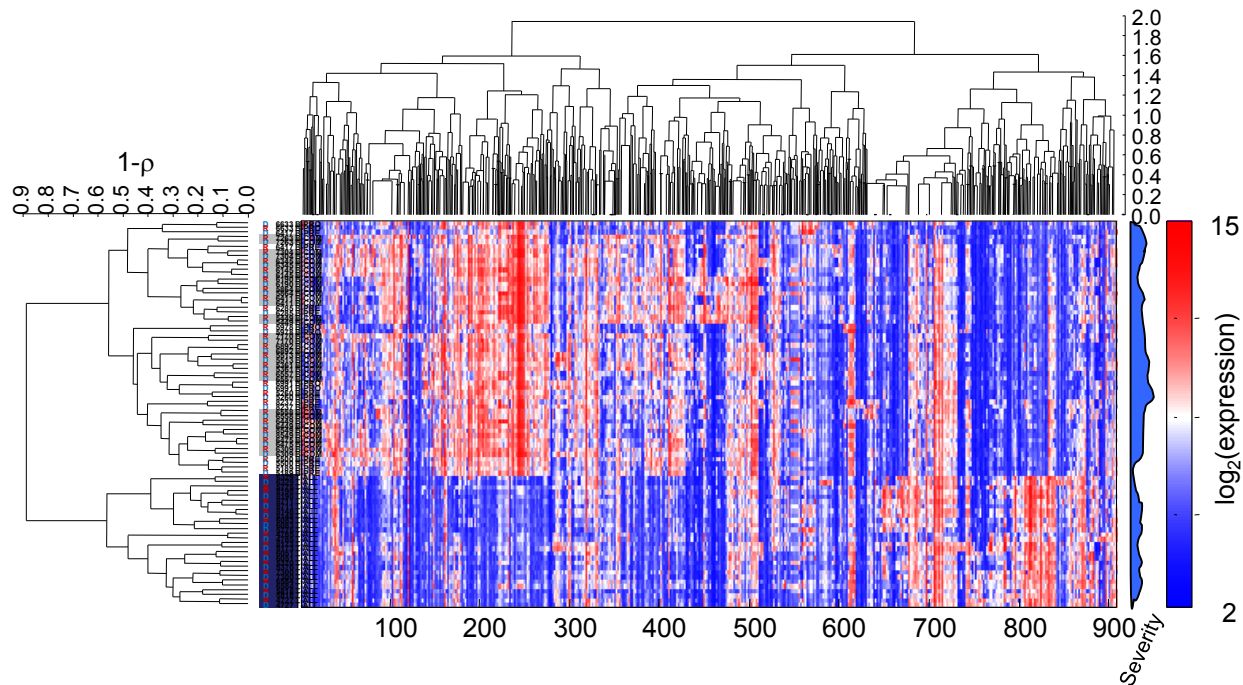
Datasets (2)

- 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)

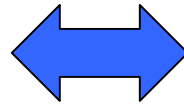
- What objects, labels/targets and features are depends on the problem...
- TFBS detection:
 - object: location on genome
 - feature: CHIP-seq, sequence features, distance to TSS ...
 - label: TFBS or not; regressor/dependent variable: specificity



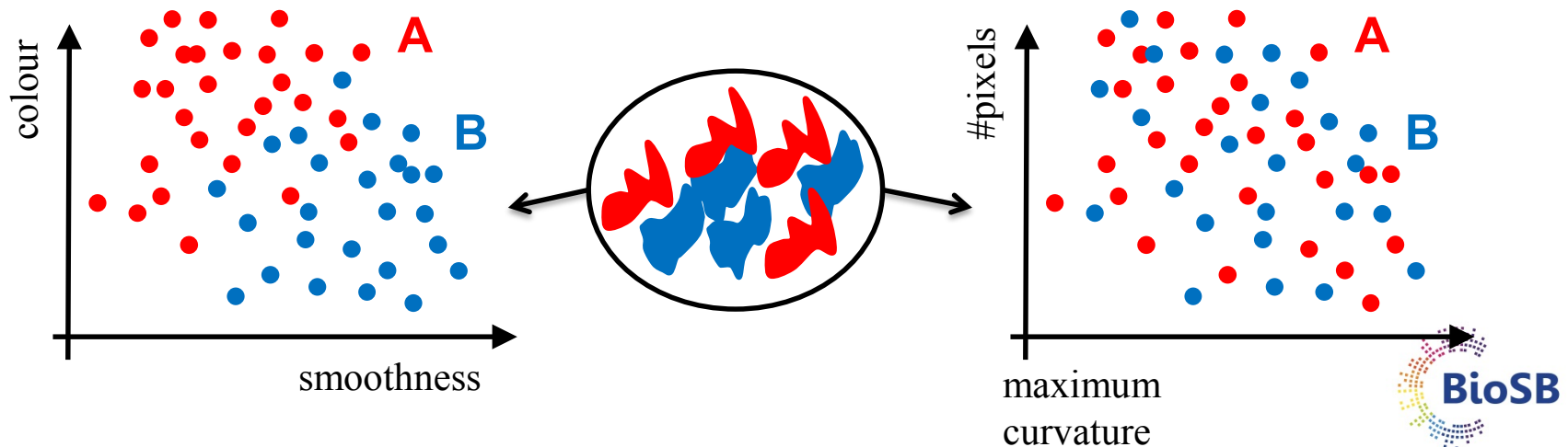
Measurements and features (3)

- Problems

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



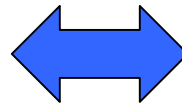
- complex
- lack of knowledge
- many poor features
- overlapping classes (classification) or highly non-linear relation (regression)



Measurements and features (3)

- Problems

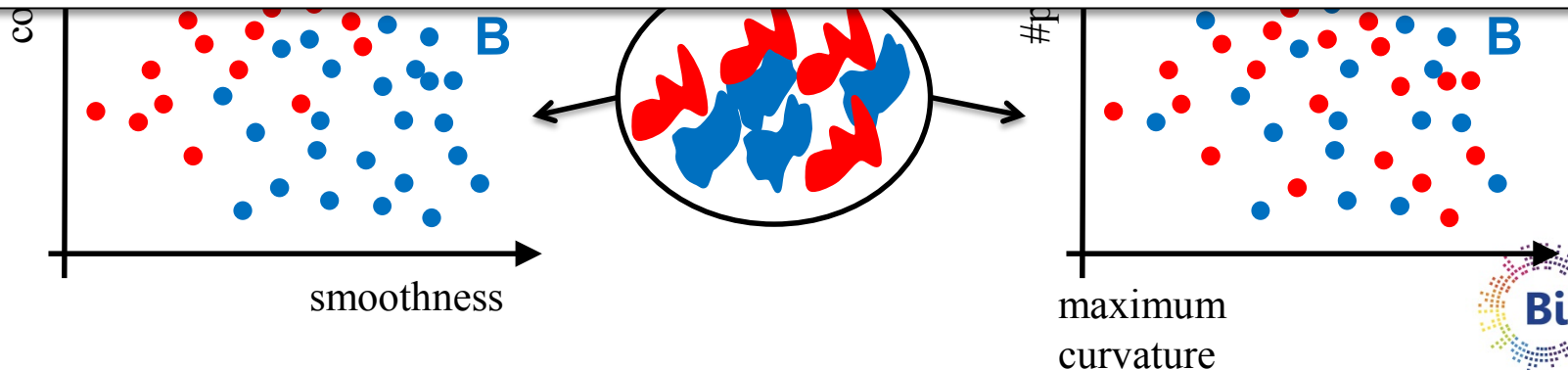
- simple
- knowledge present
- a few good features



- complex
- lack of knowledge
- many poor features

Features (object representations) are important!

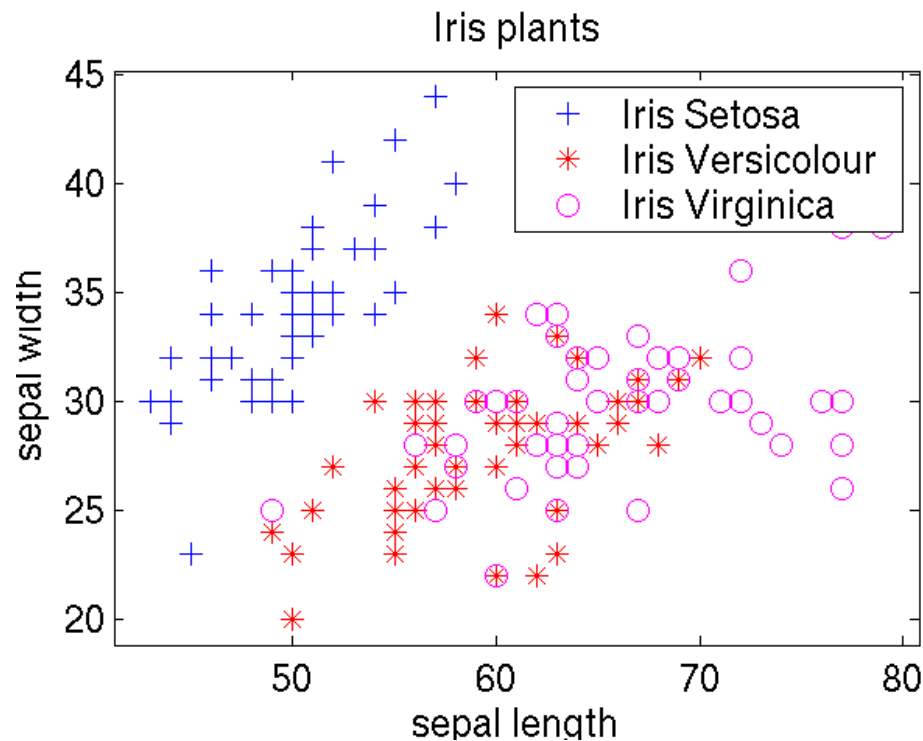
We don't deal too much with which features are measured, although we will touch upon derived features (Day 5: kernels) and learning features (Day 5: neural networks)



Feature space

- We can interpret objects as vectors in a vector space

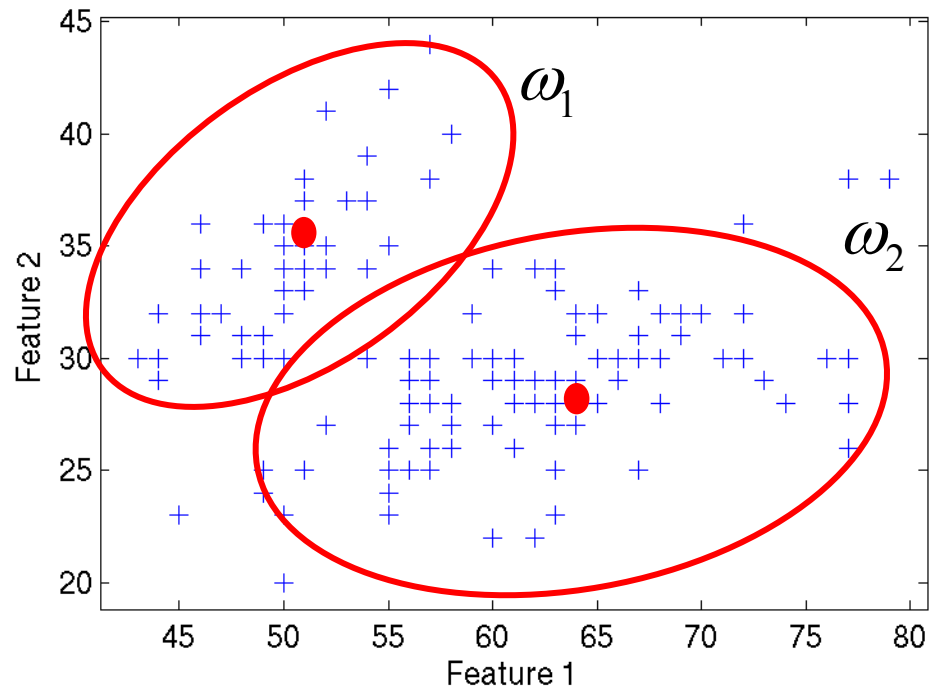
$$\mathbf{x} = [x_1, x_2, x_3, \dots, x_p]^T$$



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

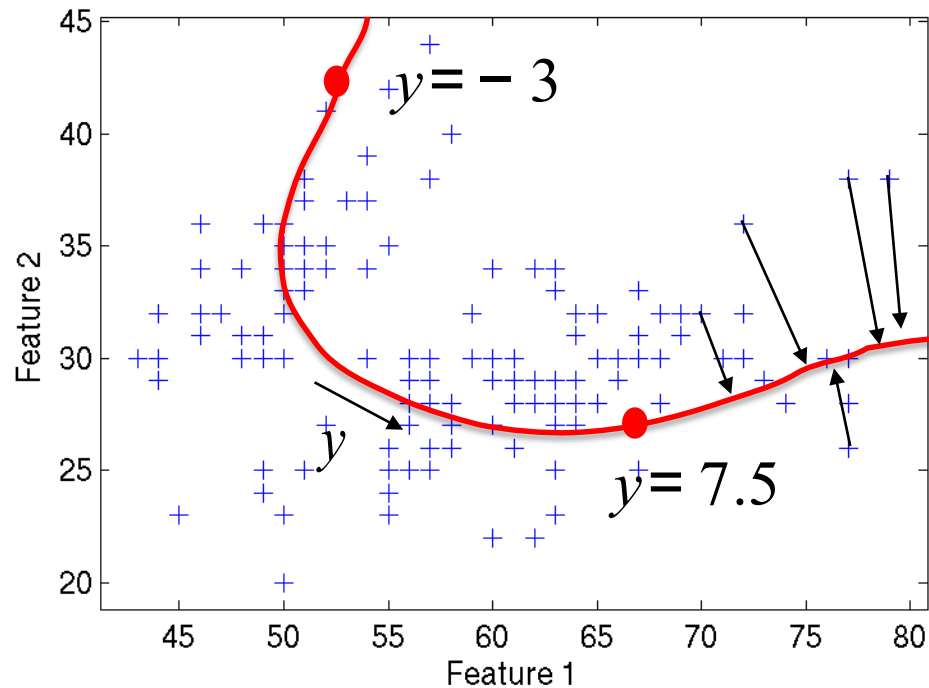
Clustering

- Given unlabeled data x ,
find labels ω for natural groups in the data



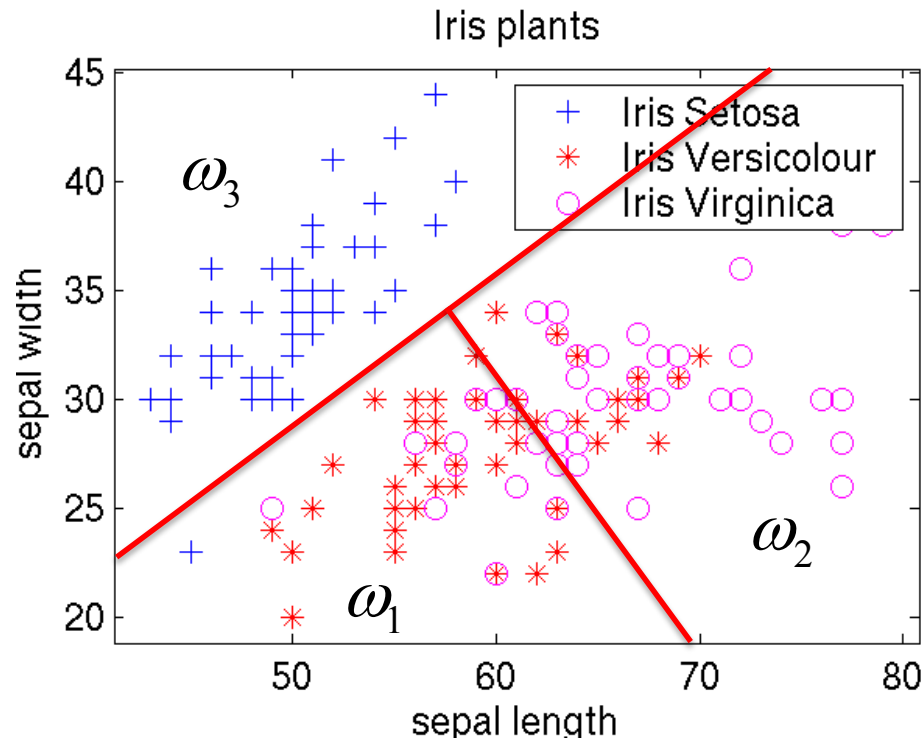
Dimensionality reduction

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



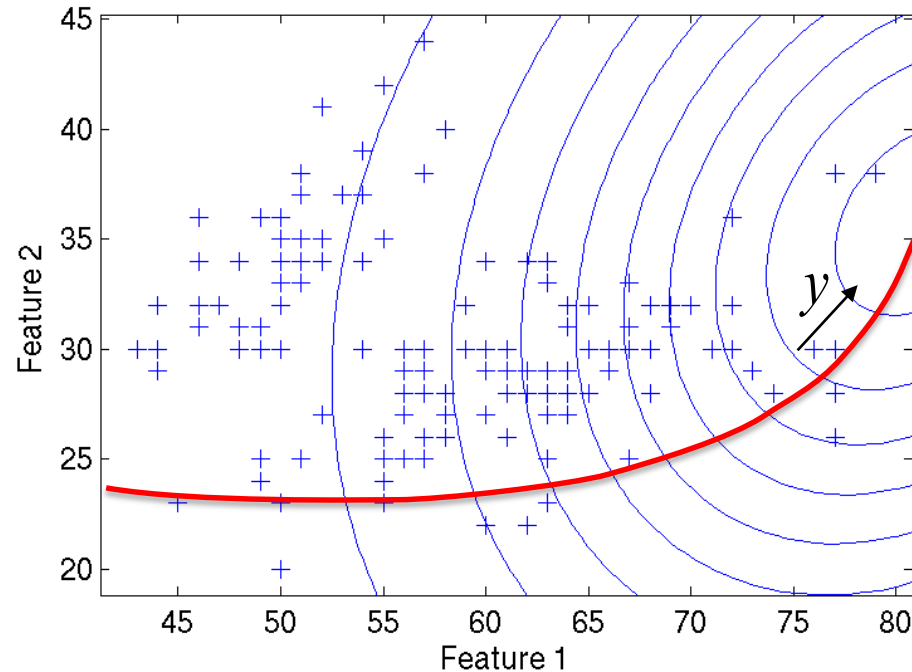
Classification

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



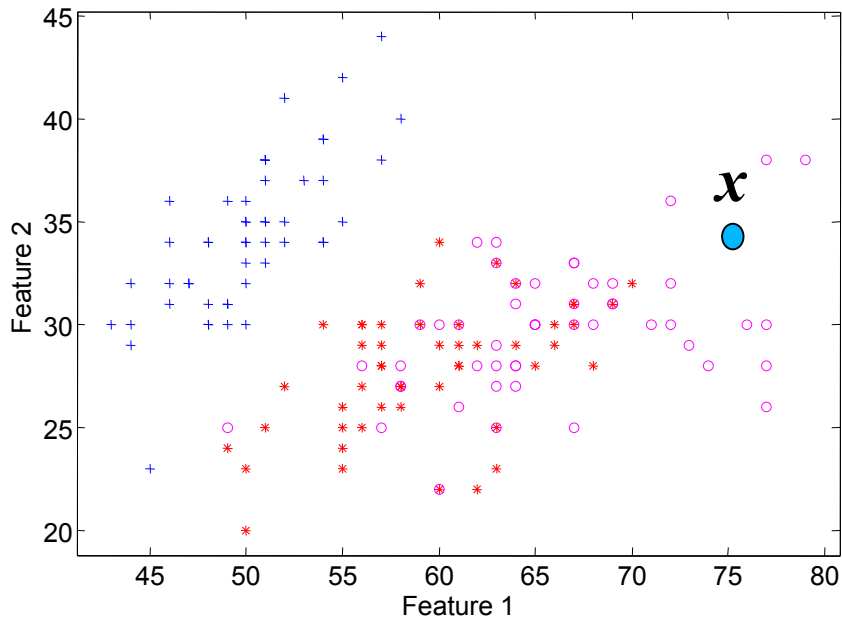
Regression

- Given labeled data x ,
assign each point in feature space a real-valued output y



General model

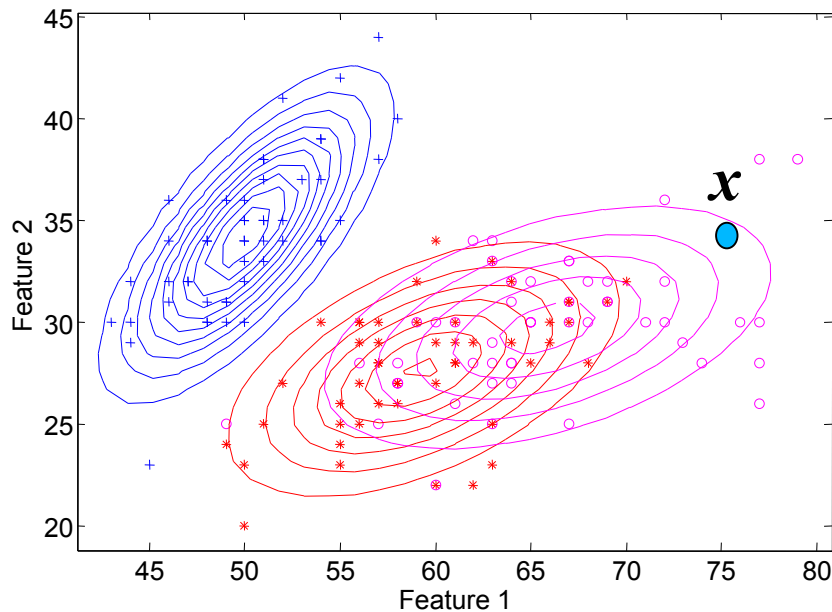
- Construct a model $f(\mathbf{x})$ that outputs ω or y
- This model should be fit to the data



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

General model (2)

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



$$p(y | \mathbf{x})$$

or

$$p(\omega | \mathbf{x})$$

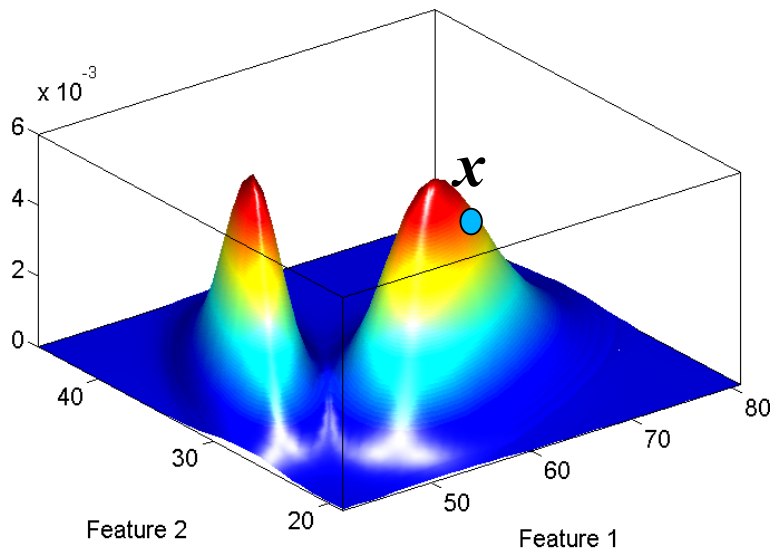


$$f(\mathbf{x}) = \omega \text{ or } f(\mathbf{x}) = y$$

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

General model (3)

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



$p(y | \mathbf{x})$
or
 $p(\omega | \mathbf{x})$



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

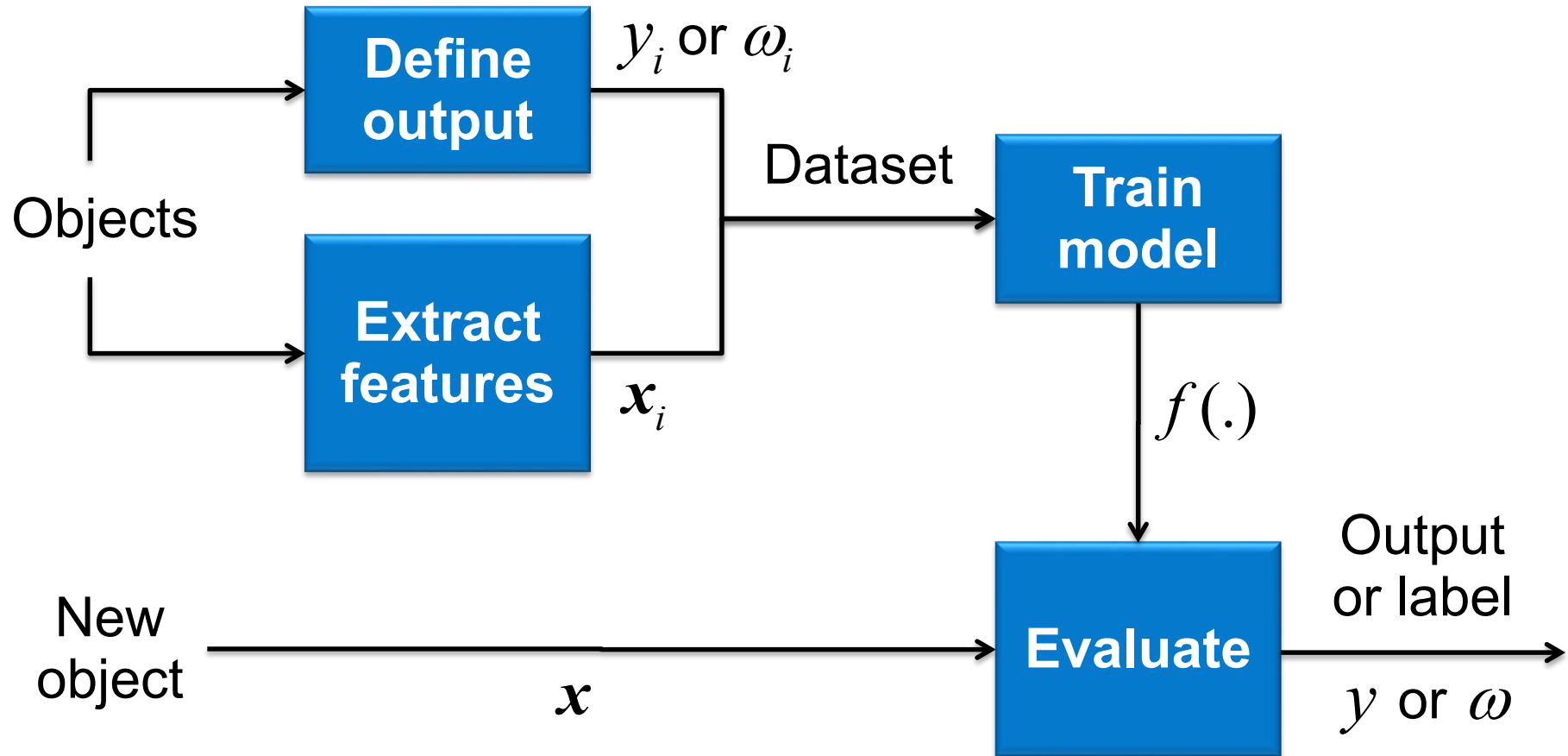
if we know the probability distributions, we can make the most informed decision



General model (4)

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

Machine learning pipeline





10min break

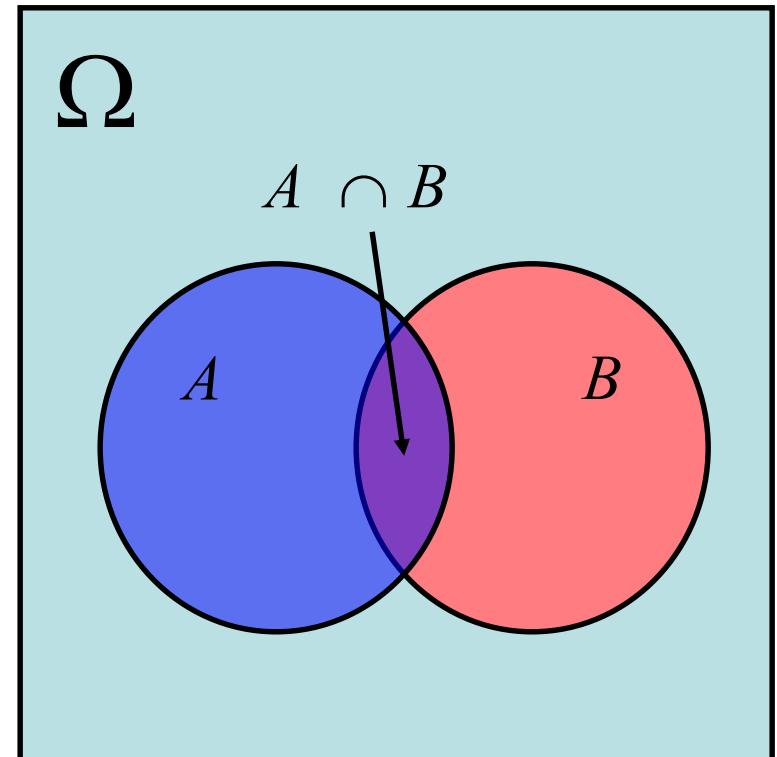
Statistics

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. $P(A) = 1/6$



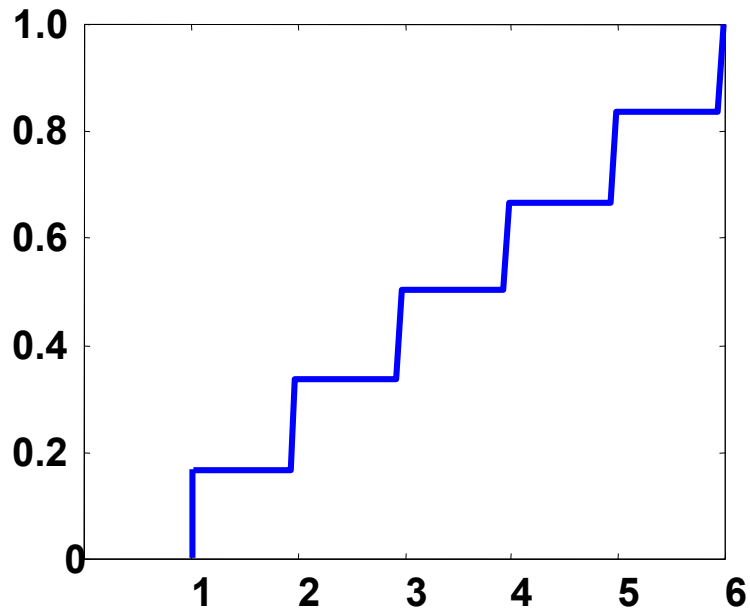
Recall: probability (3)

- 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

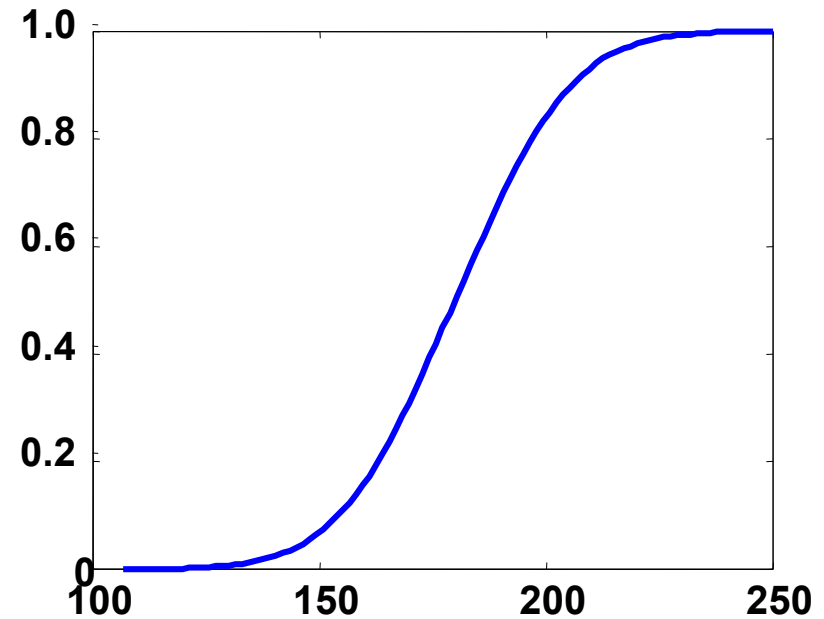
problems (can) arise in interpretation: what does it mean?

Recall: CDFs

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



e.g. 10,000 dice throws



10,000 body lengths

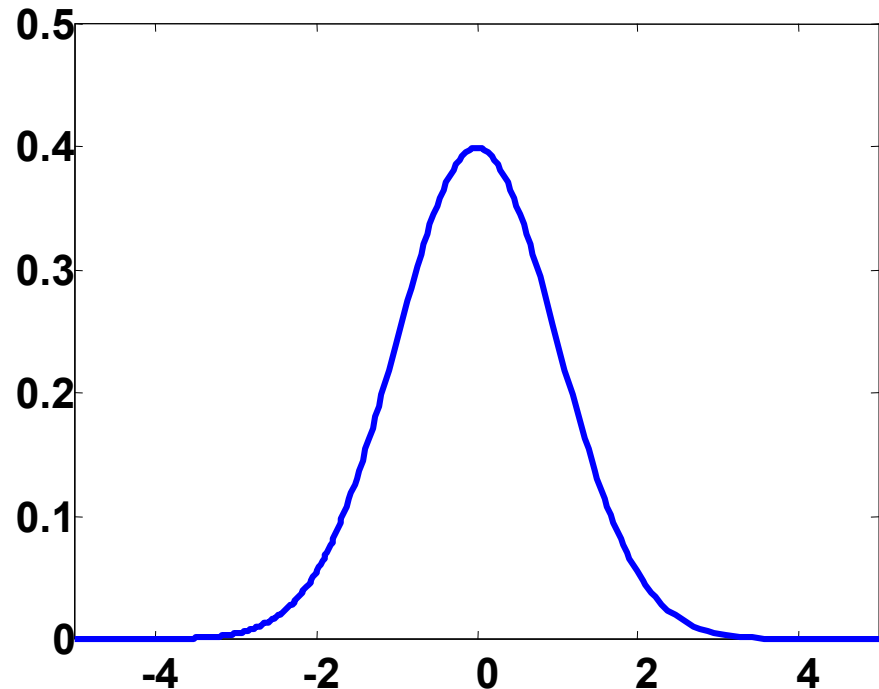
Recall: PDFs

- $p(x) = \frac{dP(x)}{dx}$: 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

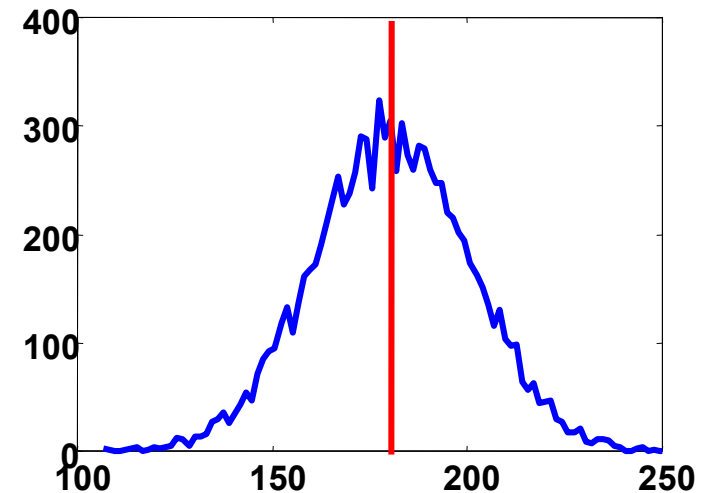
- Expectation: mean of distribution,

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

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

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

- $E[c] = c$
- $E[aX + bY] = a E[X] + b E[Y]$



*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,

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

or

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

- σ is called the standard deviation

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

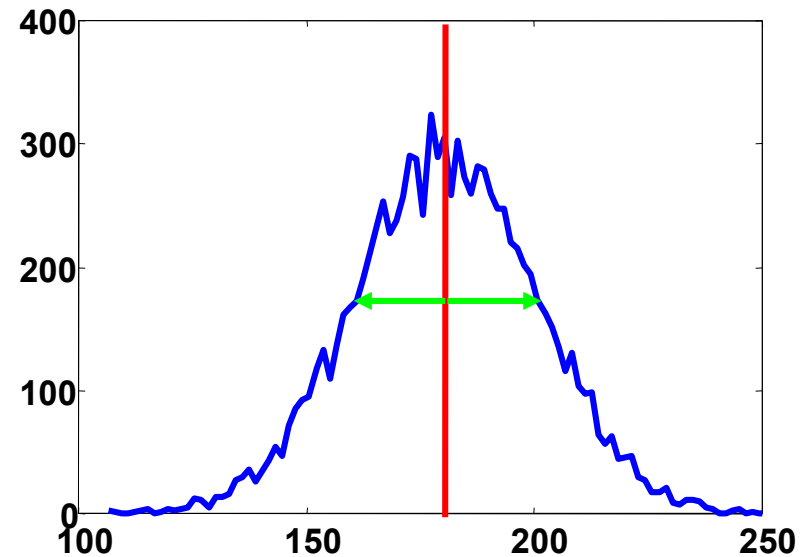
Recall: variance (2)

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

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

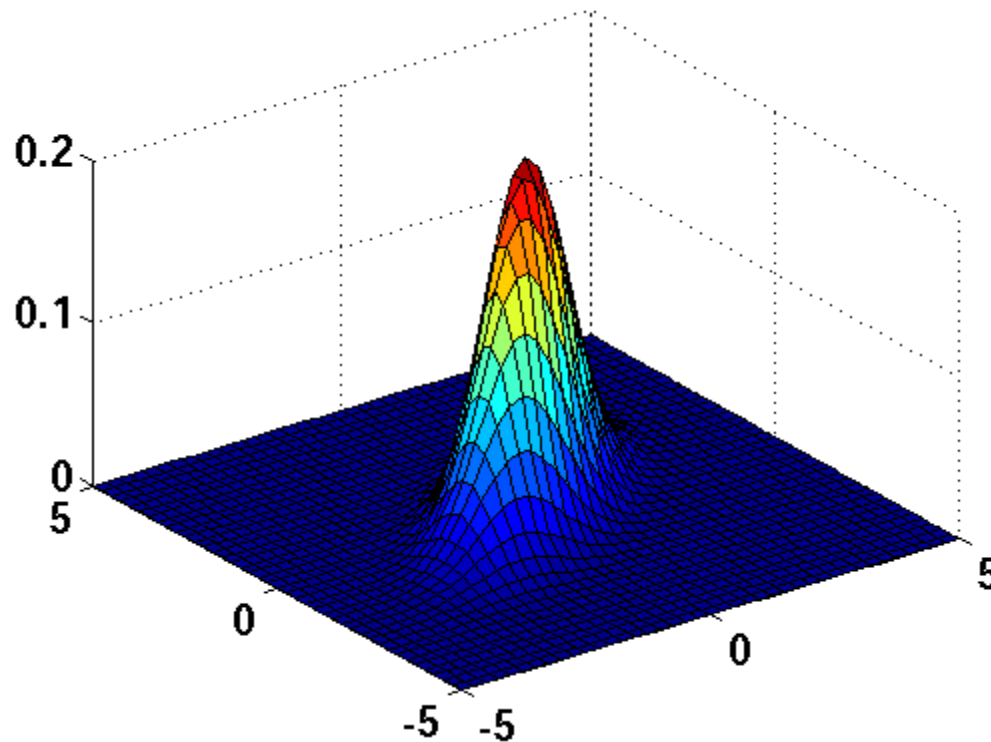
- Usually, this unbiased estimator is used:

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



Recall: joint distributions

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



Recall: covariance

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

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

- Correlation: normalised covariance,

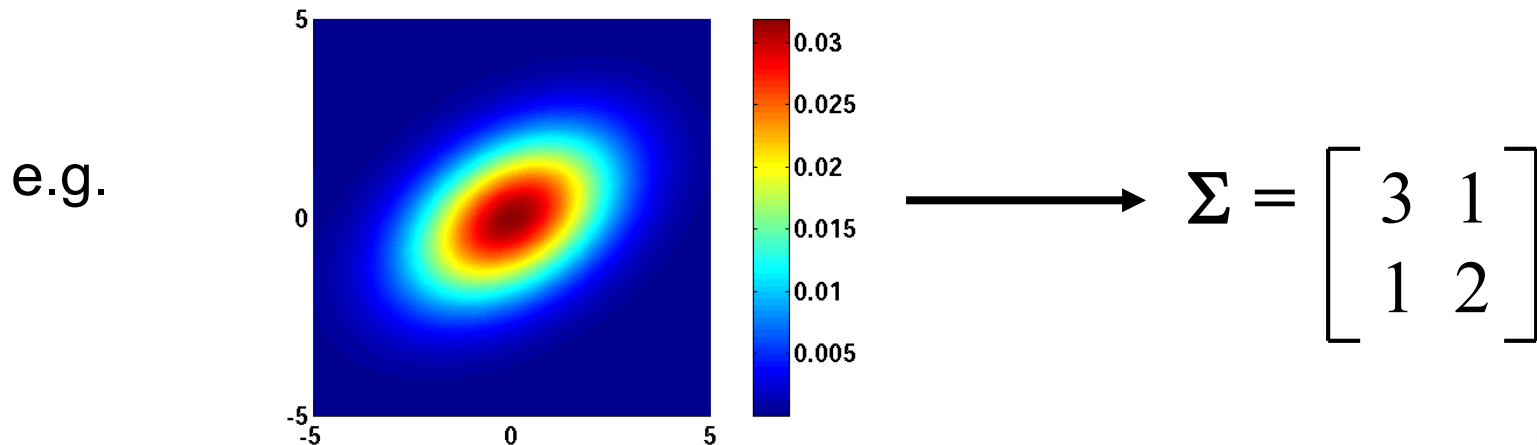
$$\rho(X, Y) = \frac{\text{cov}(X, Y)}{\sqrt{\text{var}(X)\text{var}(Y)}} \in [-1, 1]$$

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

Recall: covariance (2)

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

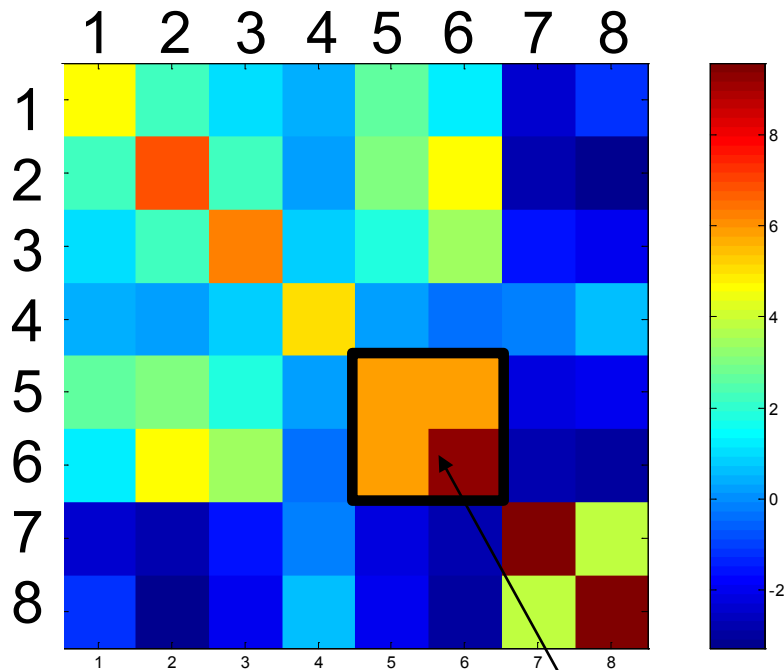
$$\Sigma = \begin{bmatrix} \text{cov}(X_1, X_1) & \text{cov}(X_1, X_2) & \dots & \text{cov}(X_1, X_p) \\ \text{cov}(X_2, X_1) & \dots & \dots & \text{cov}(X_2, X_p) \\ \dots & \dots & \dots & \dots \\ \text{cov}(X_p, X_1) & \text{cov}(X_p, X_2) & \dots & \text{cov}(X_p, X_p) \end{bmatrix}$$



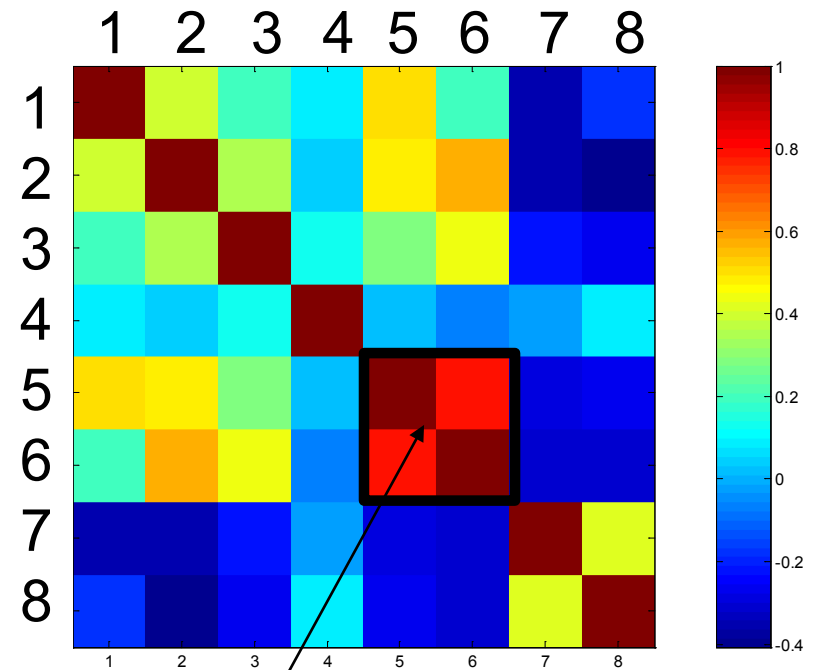
Pairwise covariance of all features!

Recall: covariance (3)

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



`imagesc(cov(+a))`

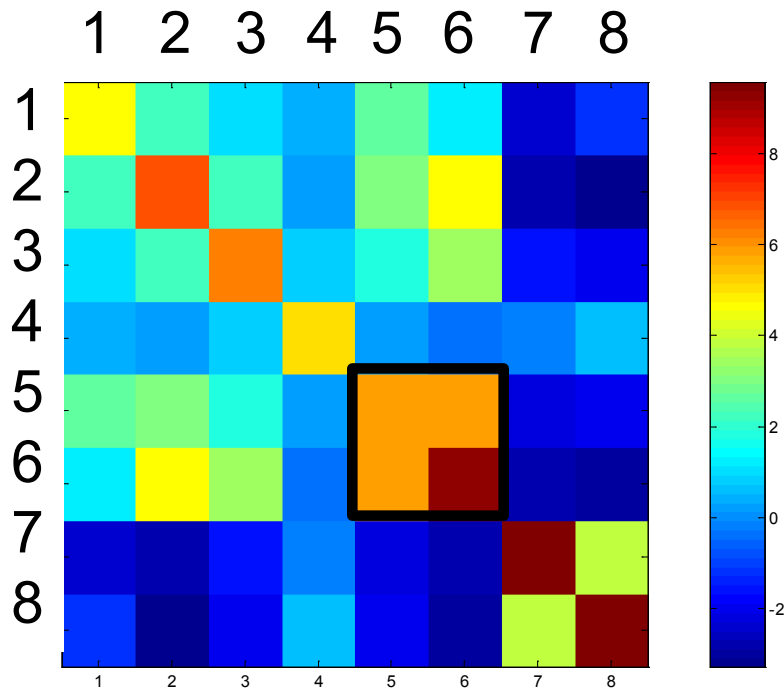


`imagesc(corrcoef(+a))`

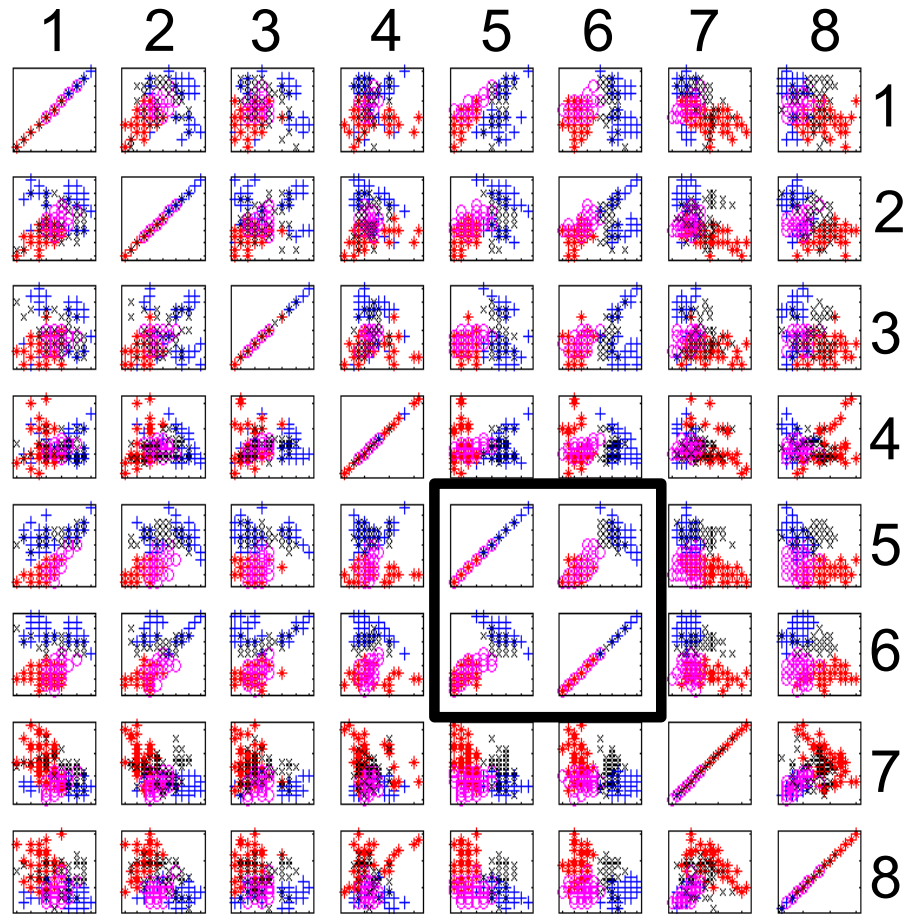
characters 5/6 are alike

Recall: covariance (4)

- Example: IMOX data



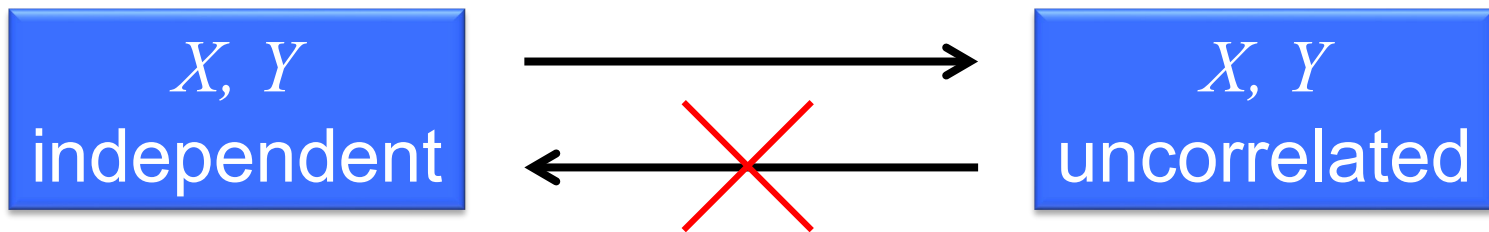
```
imagesc(cov(+a))
```



```
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
$$p(x,y) = p(x) p(y)$$



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

Recall: Bayes' theorem

- Conditional probability of A given B ,

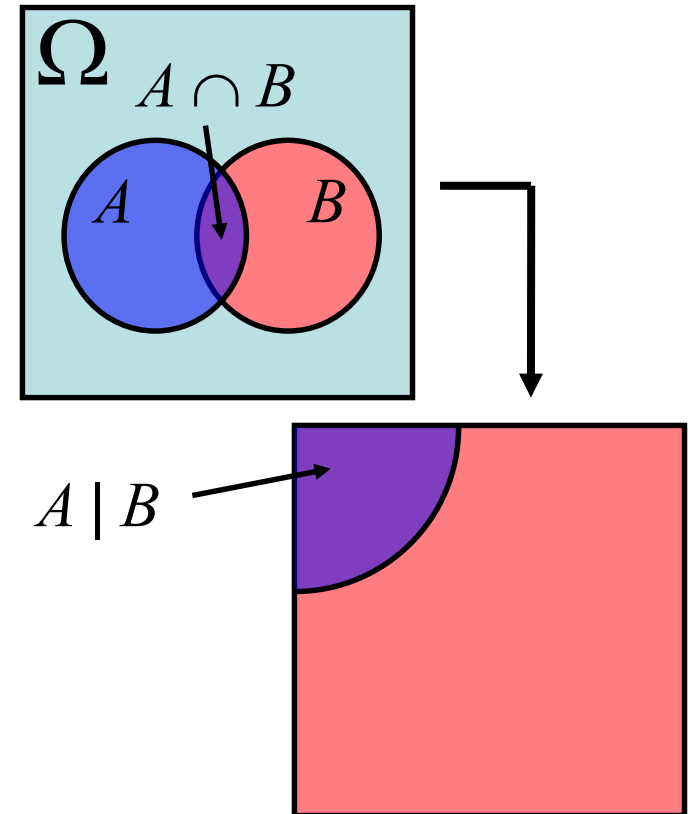
$$P(A | B) = \frac{P(A \cap B)}{P(B)}$$

- 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)

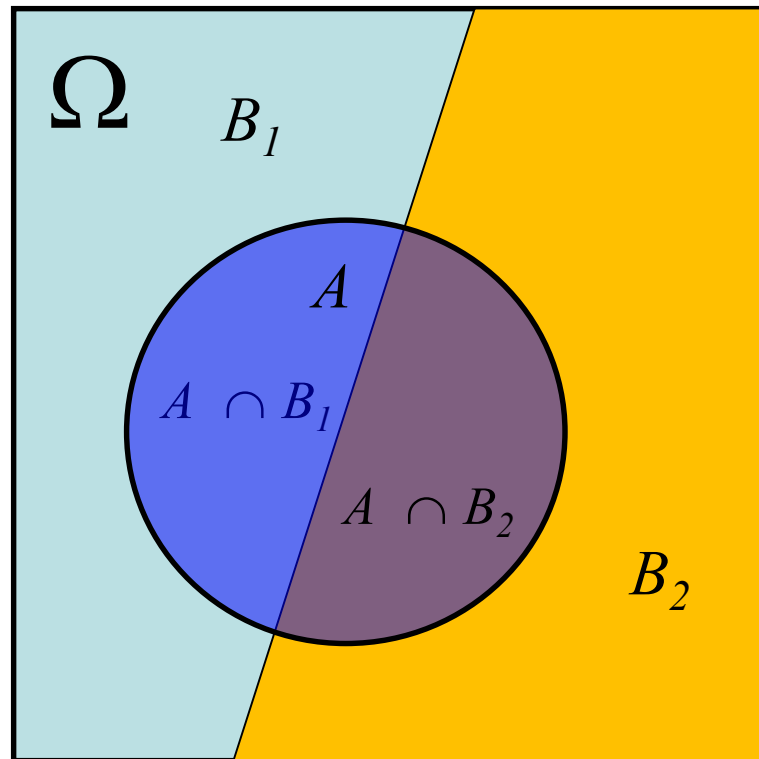
- Bayes' theorem is very useful, but controversial:
 - reverses causality
 - introduces subjective (prior) probabilities

$$P(\textit{cause} | \textit{effect}) = \frac{P(\textit{effect} | \textit{cause})P(\textit{cause})}{P(\textit{effect})}$$

- **... but the cornerstone of pattern recognition and machine learning**
 - $P(\textit{disease} | \textit{temperature}) = \frac{P(\textit{temperature} | \textit{disease})P(\textit{disease})}{P(\textit{temperature})}$
 - 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 $p(y | x)$ 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, ...

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

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

Bayes' theorem (5)

- Classification example $p(\omega | \mathbf{x})$:
 - $\omega \in \{ \text{'man'}, \text{'woman'} \} = \text{label}$
 - $x \in \mathbb{R}^1 = \text{height measurement(m)}$
- $p(\omega)$: 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):

$$p(x) = \sum_i p(x | \omega_i) p(\omega_i)$$

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

Bayes' theorem (6)

- Regression example $p(y | x)$:
 - $y \in \mathbb{R}^1 =$ outside temperature ($^{\circ}\text{C}$)
 - $x \in \mathbb{R}^1 =$ thermometer measurement ($^{\circ}\text{C}$)
- $p(y)$: 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:

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

*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 :

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

*Risk of saying y' = integral over **all possible situations**:*

*Remember total probability: $P(r) = \text{SUM_all_y} \{ P(r|y)p(y) \}$
 $= \text{SUM_all_y} \{ P(r \text{ and } y) \}$*

Bayesian estimation (2)

- Optimal prediction:

$$\begin{aligned}\hat{y} &= \arg \min_{y'} r(y' | x) \\ &= \arg \min_{y'} \int \Lambda(y', y) p(y | x) dy\end{aligned}$$

- Bayesian estimation: minimize overall risk

$$r^* = E[r(\hat{y} | x)] = \int r(\hat{y} | x) p(x) dx$$

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

- $\omega = \{ h, d \}$ (healthy, diseased)

- $\Lambda(\omega', \omega) =$

	$\omega = h$	$\omega = d$
$\omega' = h$	0	1
$\omega' = d$	1	0

- Say the system predicts $p(\omega = d|x) = 0.05$, then

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

$$= p(\omega = d|x) = 0.05$$

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

$$= p(\omega = h|x) = 0.95$$

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

$p(\omega = h|x) = 0.95$
(by definition)

Bayesian estimation (4)

- Example: diagnostic system

- $\omega = \{ h, d \}$ (healthy, diseased)

- $\Lambda(\omega', \omega) =$

	$\omega = h$	$\omega = d$
$\omega' = h$	0	25
$\omega' = d$	1	0

- Say the system predicts $p(\omega = d|x) = 0.05$, then

$$\begin{aligned} r(\omega' = h|x) &= \Lambda(h,h) p(\omega=h|x) + \Lambda(h,d) p(\omega=d|x) \\ &= 0 \cdot 0.95 + 25 \cdot 0.05 = 1.25 \end{aligned}$$

$$\begin{aligned} r(\omega' = d|x) &= \Lambda(d,h) p(\omega=h|x) + \Lambda(d,d) p(\omega=d|x) \\ &= 1 \cdot 0.95 + 0 \cdot 0.05 = 0.95 \end{aligned}$$

- *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

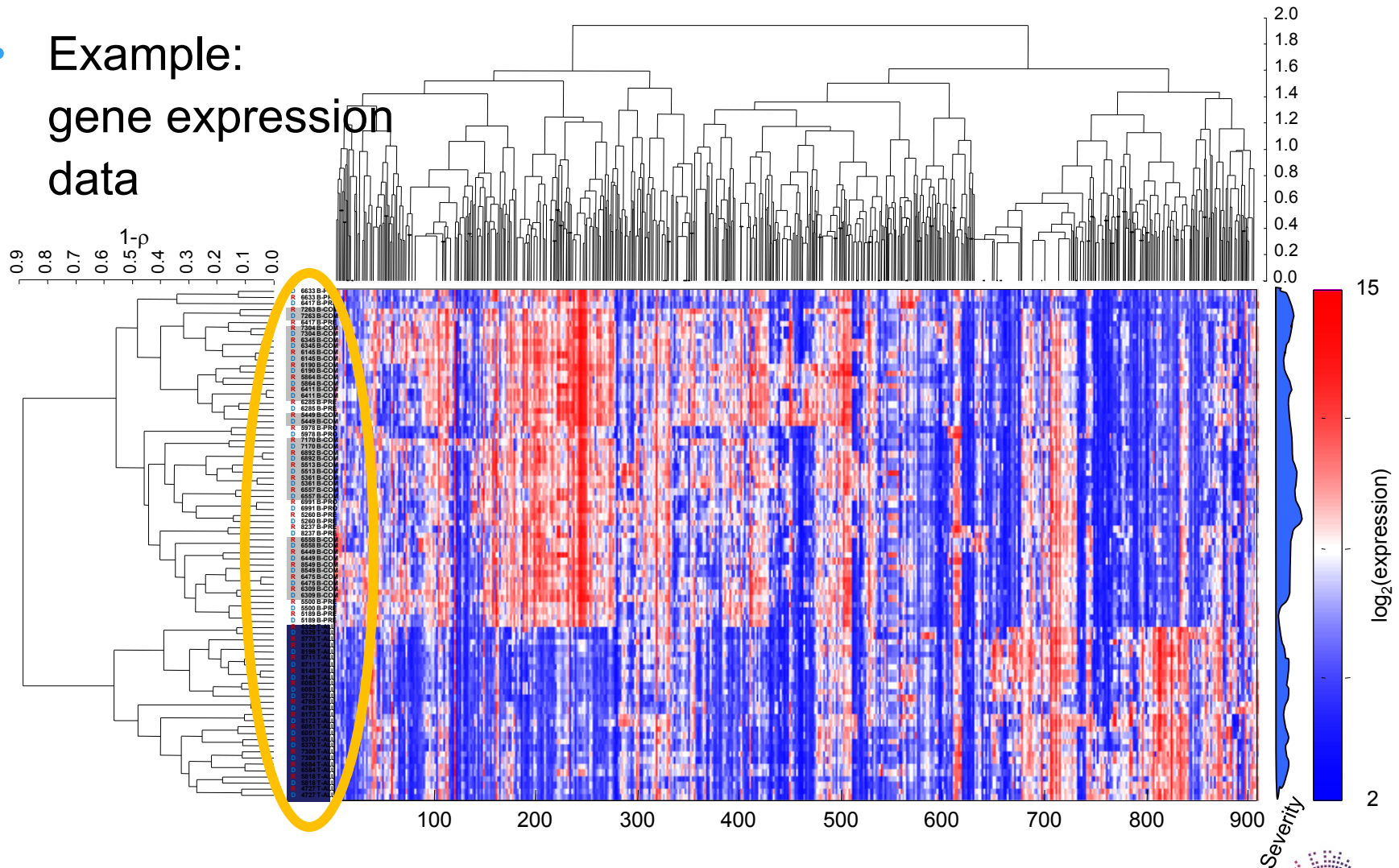


10min break

Bayesian classification

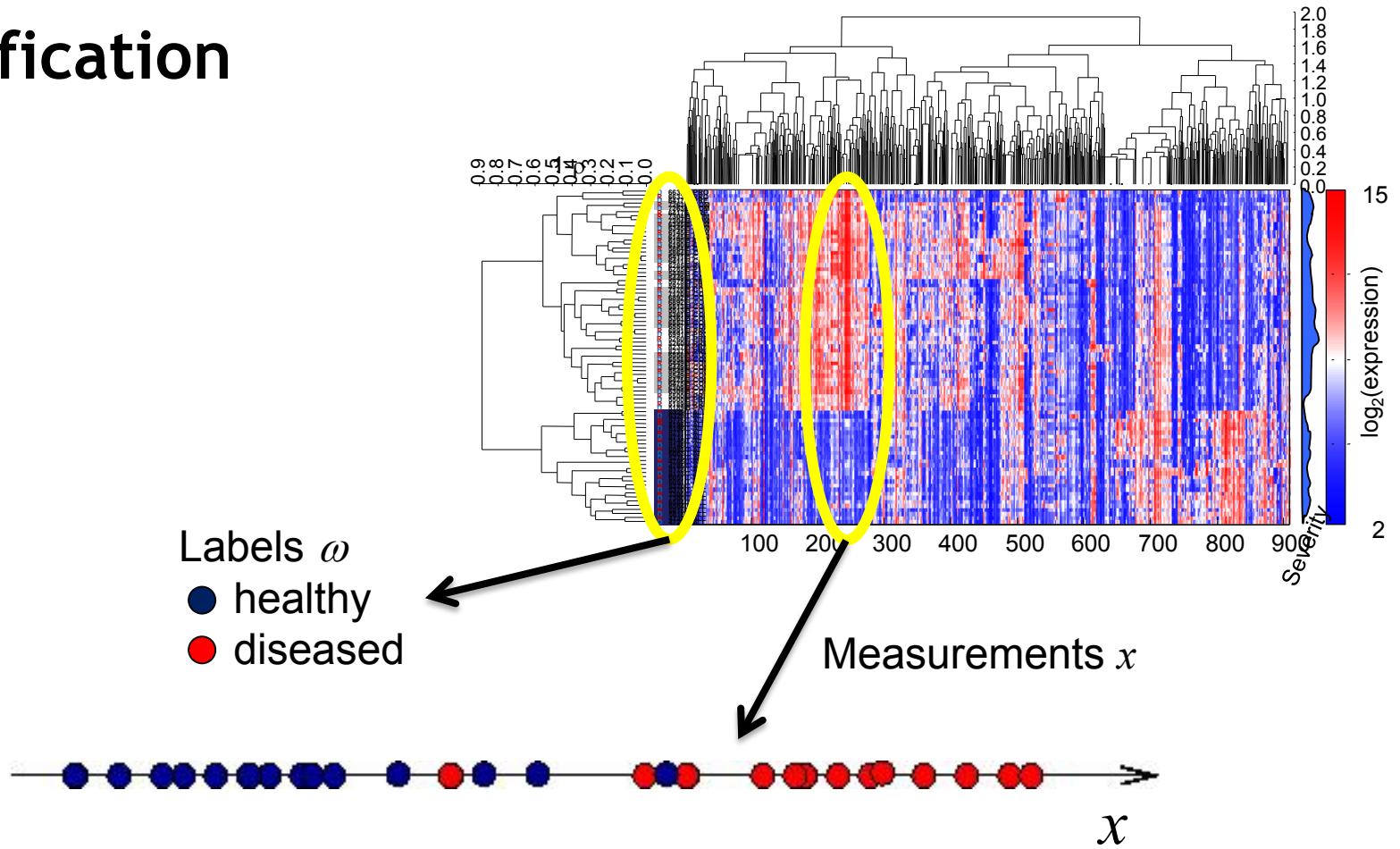
Classification in bioinformatics

- Example:
gene expression
data



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

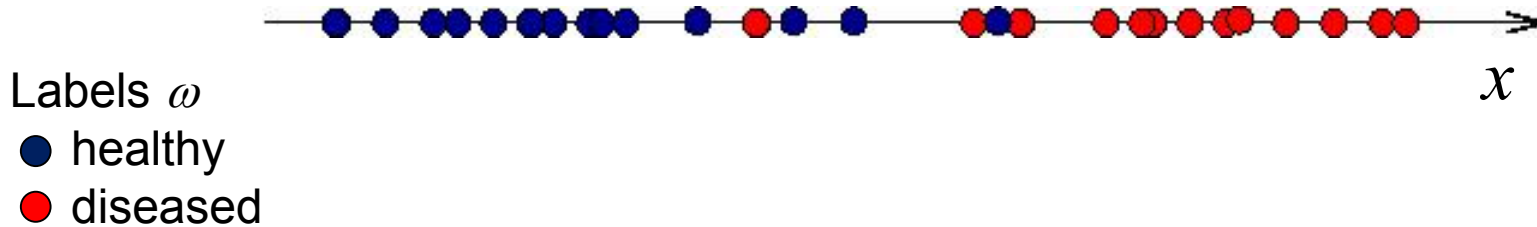
Classification



As example, consider a single gene expression measurement x

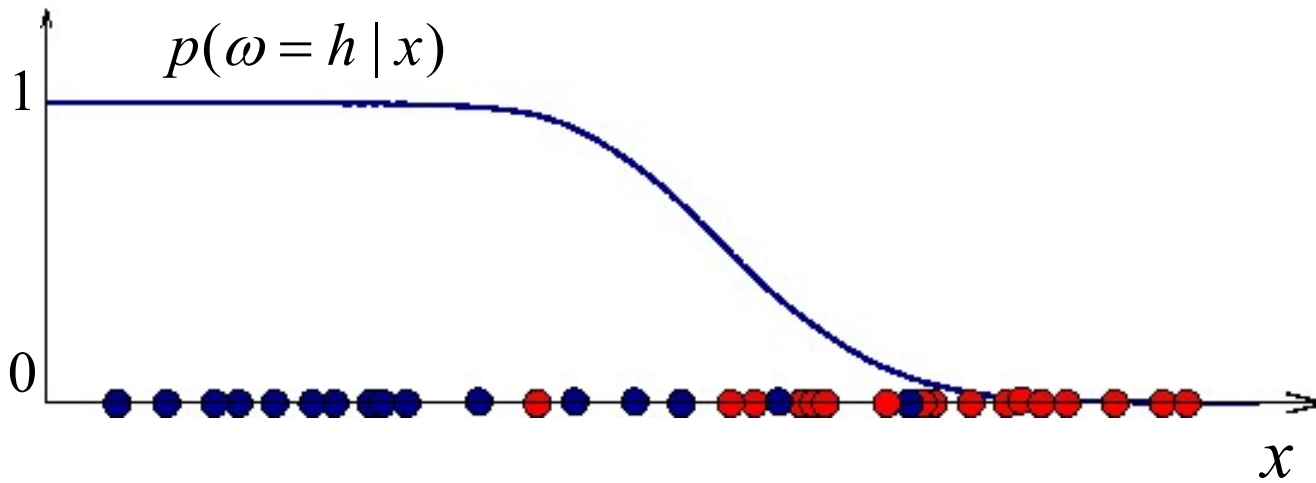
Posterior probability

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



Posterior probability (2)

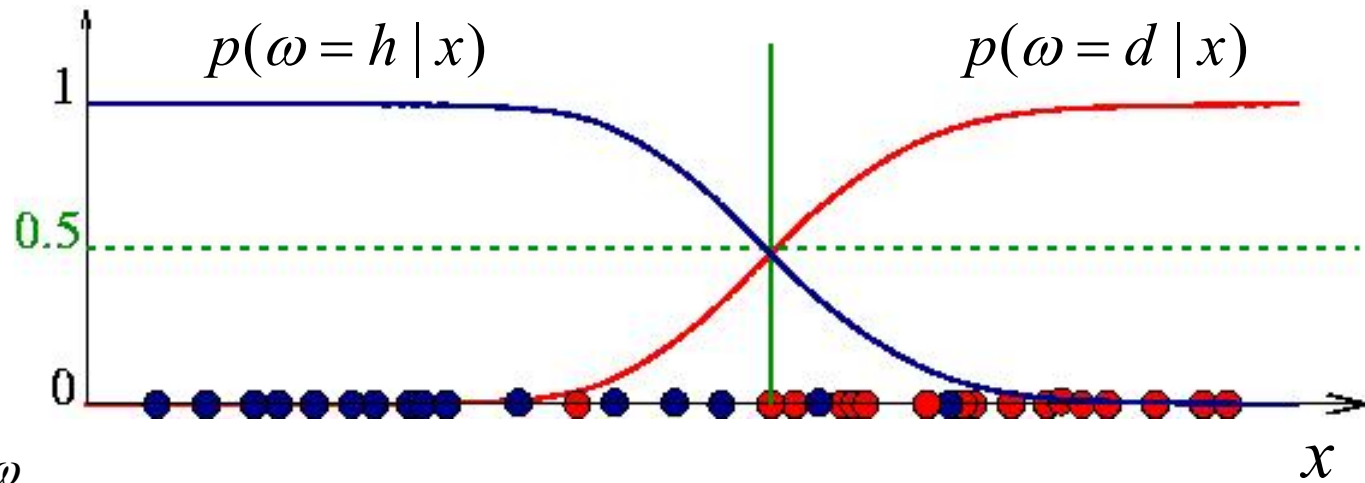
- For each object, we have to estimate $p(\omega|x)$ or $p(y|x)$



Labels ω
● healthy
● diseased

Posterior probability (2)

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



Labels ω

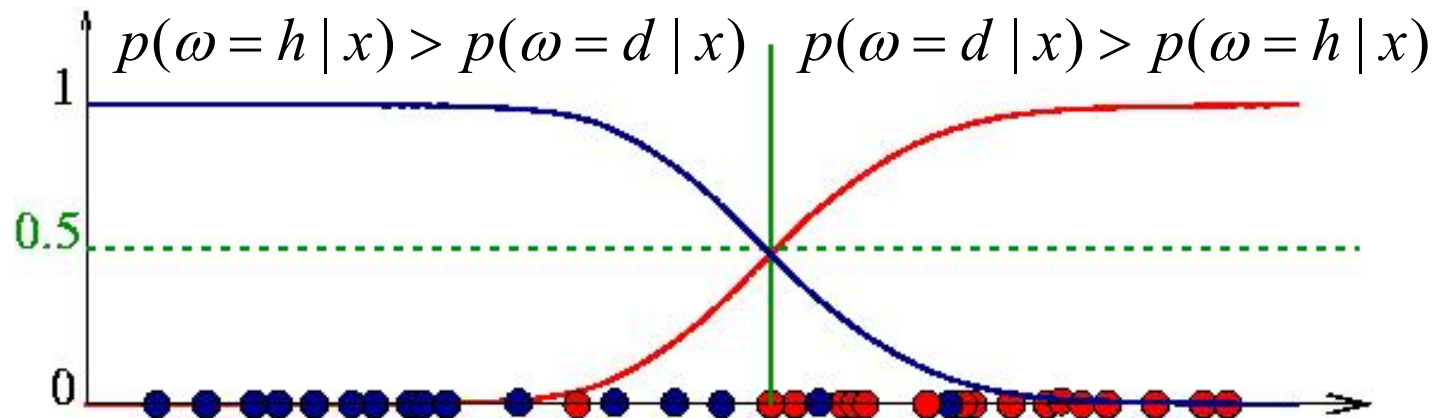
● healthy

● diseased

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

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 $p(\omega = h | x) > p(\omega = d | x)$ then assign to h
otherwise to d
 - if $p(\omega = h | x) - p(\omega = d | x) \geq 0$ then assign to h
otherwise to d
 - if $\frac{p(\omega = h | x)}{p(\omega = d | x)} \geq 1$ then assign to h
otherwise to d
 - if $\ln[p(\omega = h | x)] - \ln[p(\omega = d | x)] \geq 0$ 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:
$$p(\omega = c | x) = \frac{p(x | \omega = c)p(\omega = c)}{p(x)}$$

- class-conditional distribution: $p(x | \omega = c)$

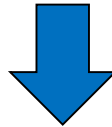
- prior distribution: $p(\omega)$

- data distribution:
$$p(x) = \sum_{c=1}^C p(x | \omega = c)p(\omega = c)$$

Bayes' rule (2)

- The decision rule becomes

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



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



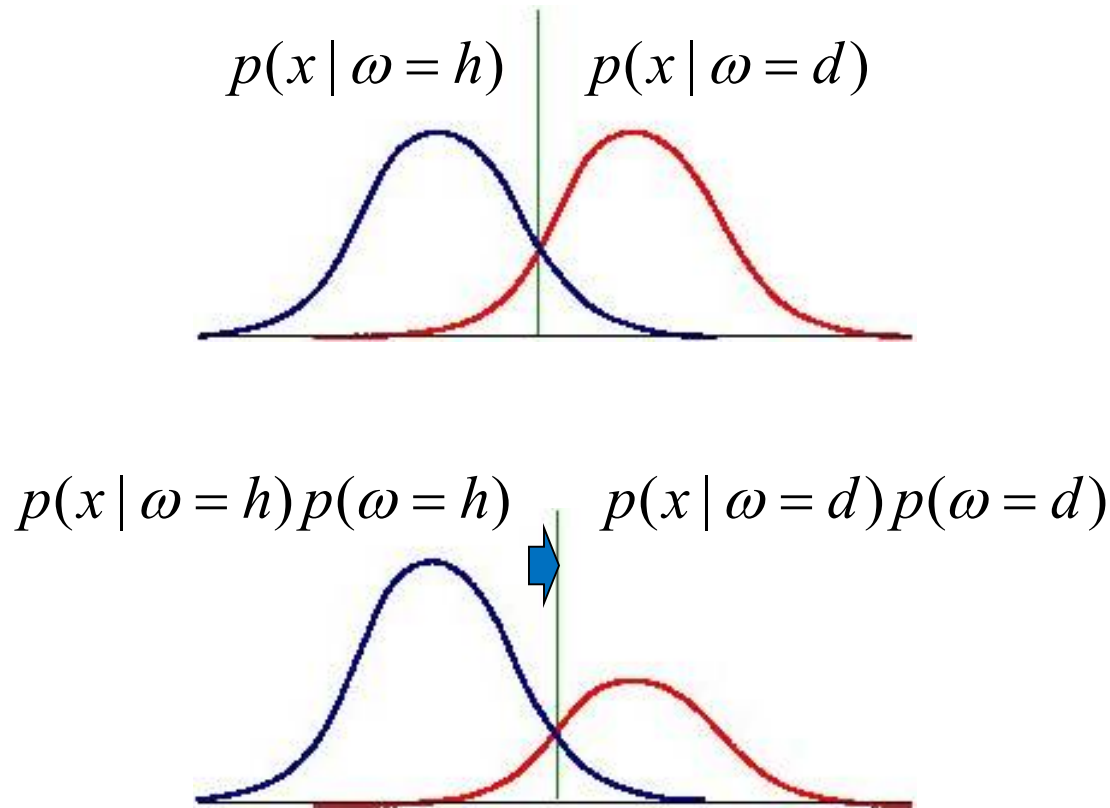
$$p(x | \omega = h)p(\omega = h) > p(x | \omega = d)p(\omega = d)$$

Seems trivial, but this is something we can measure!



Bayes' rule (3)

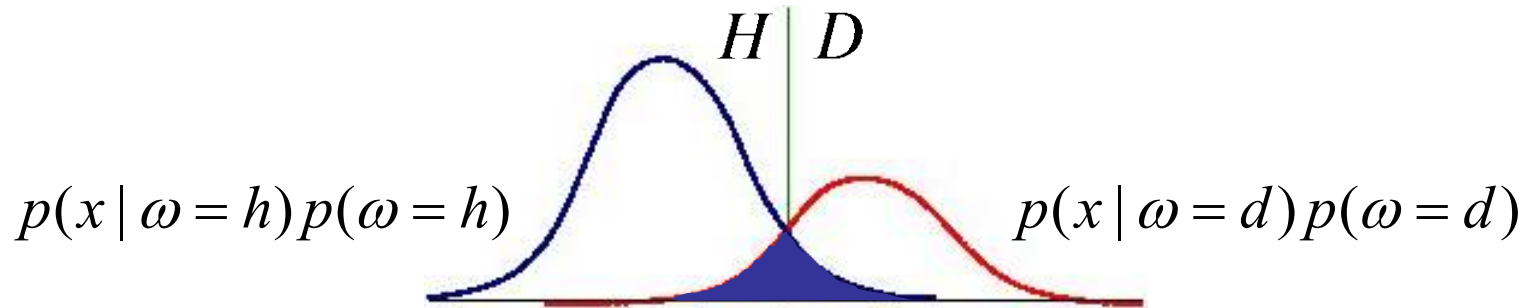
- The effect of the prior:



*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)

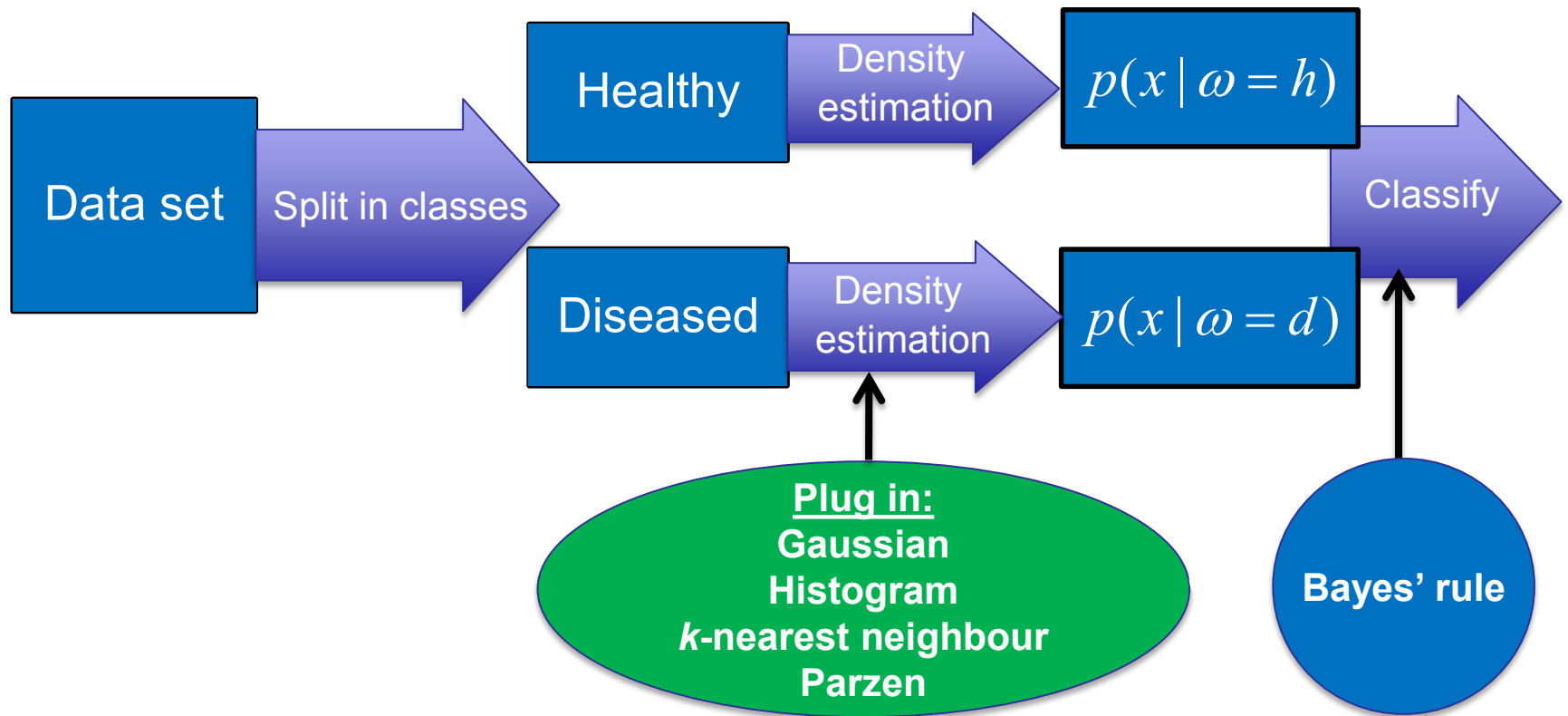
- Bayes' error: ***minimal attainable error***
(if data follows class-conditional contributions...)



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

Bayes' rule (5)

- In practice:



Density estimation

Plug-in Bayes classifier

- Bayes' rule:

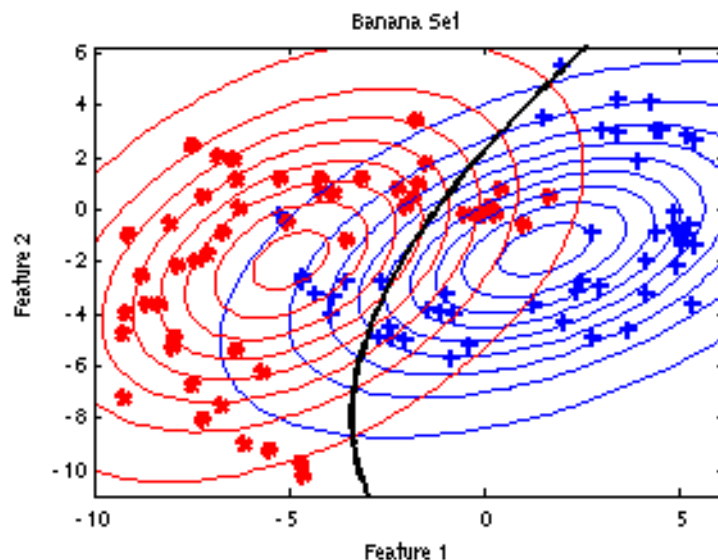
$$c_{opt} = \arg \max_c p(\omega = c | x) = \arg \max_c p(x | \omega = c) p(\omega = c)$$

- 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 $\hat{p}(x | \omega = c)$ 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*

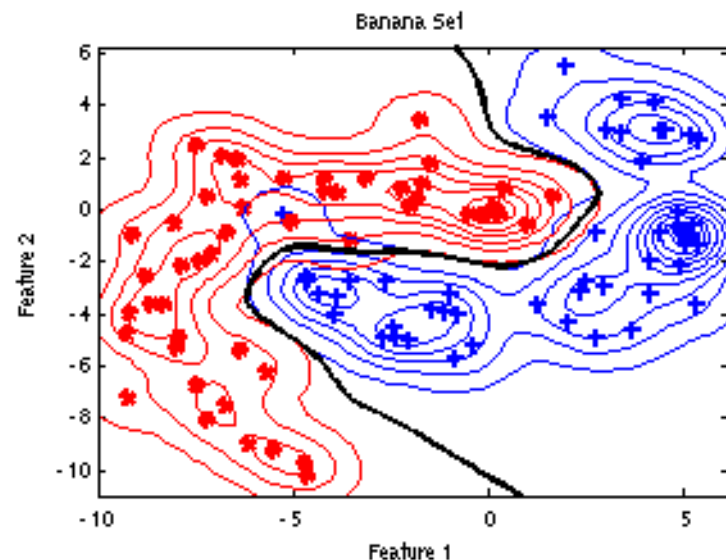
Plug-in Bayes classifier (2)

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

Normal density estimation



Parzen density estimation



Which one is best (Parzen)

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

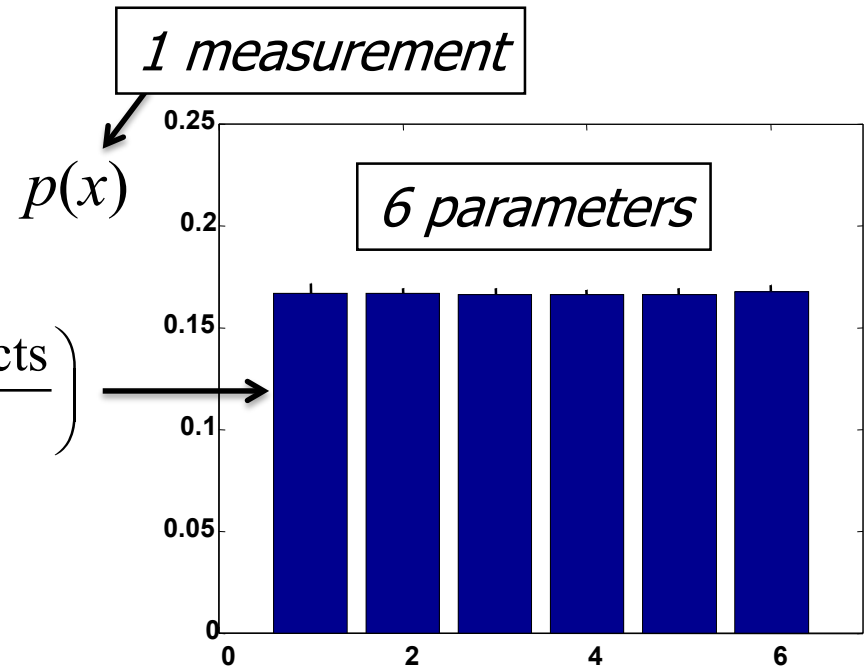
Density estimation

- Simplest approach: approximate density by histogram

e.g. 10,000 throws
of a dice

10,000 objects

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

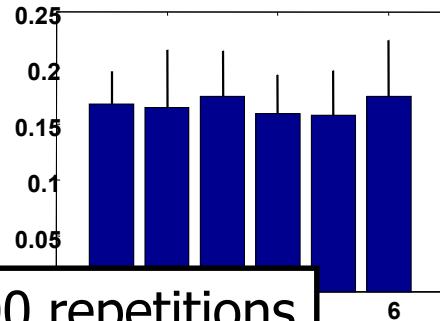


- But...

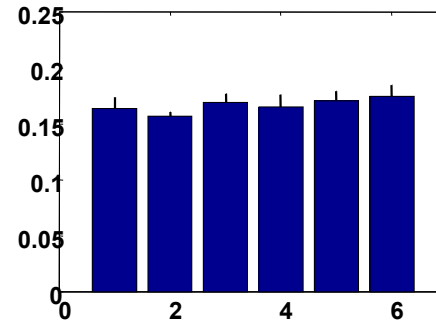
Density estimation (2)

- Problem: accuracy

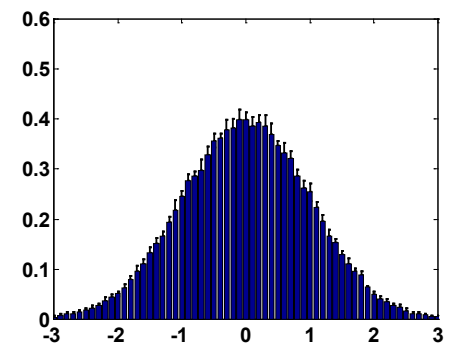
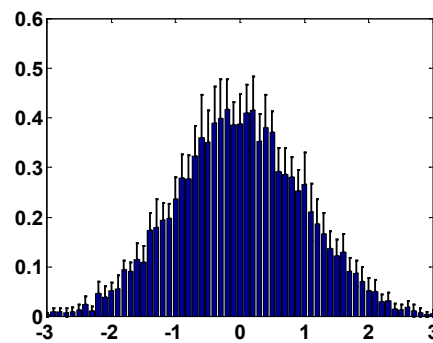
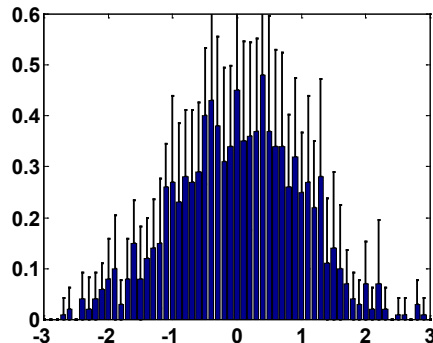
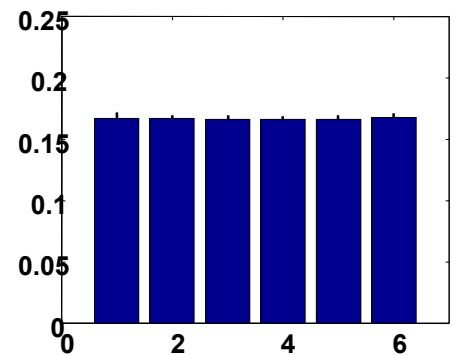
100 objects



1,000 objects



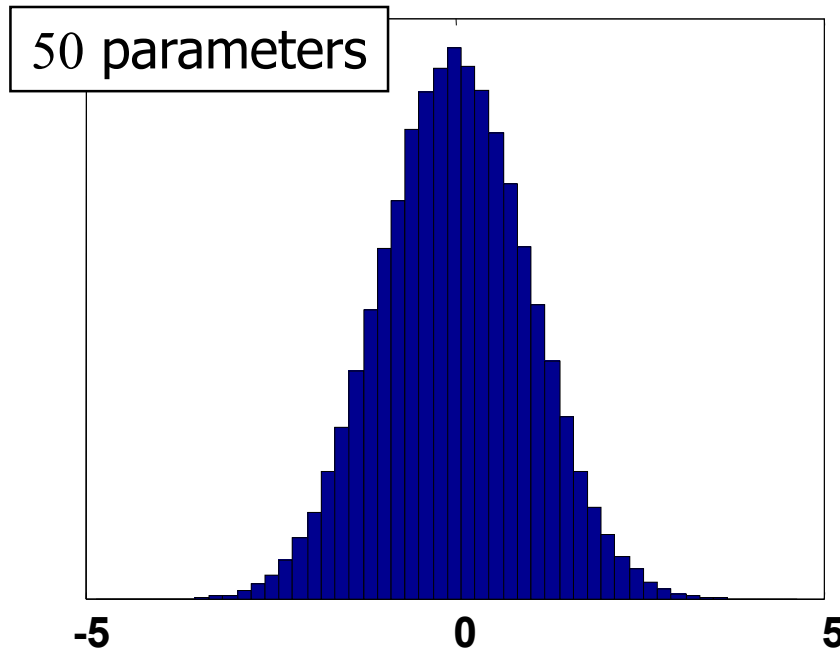
10,000 objects



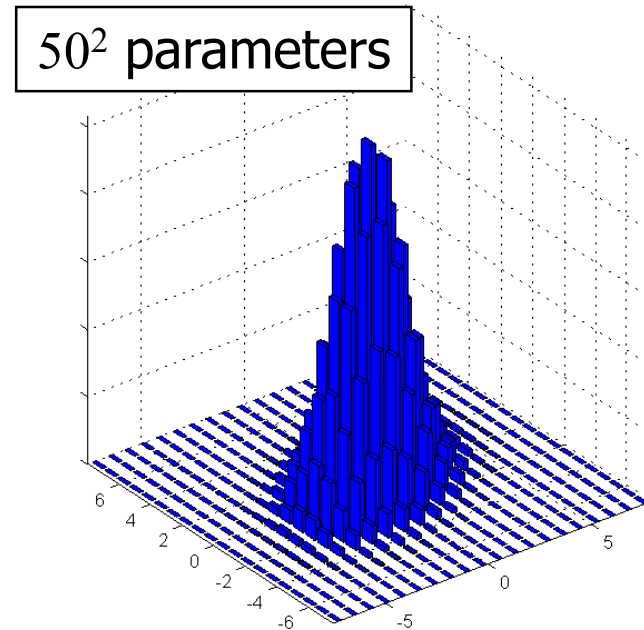
Gauss: 50 bin \rightarrow 50 parameters to estimate

Density estimation (3)

- For 1 - dimensional data, ± 1000 points needed



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

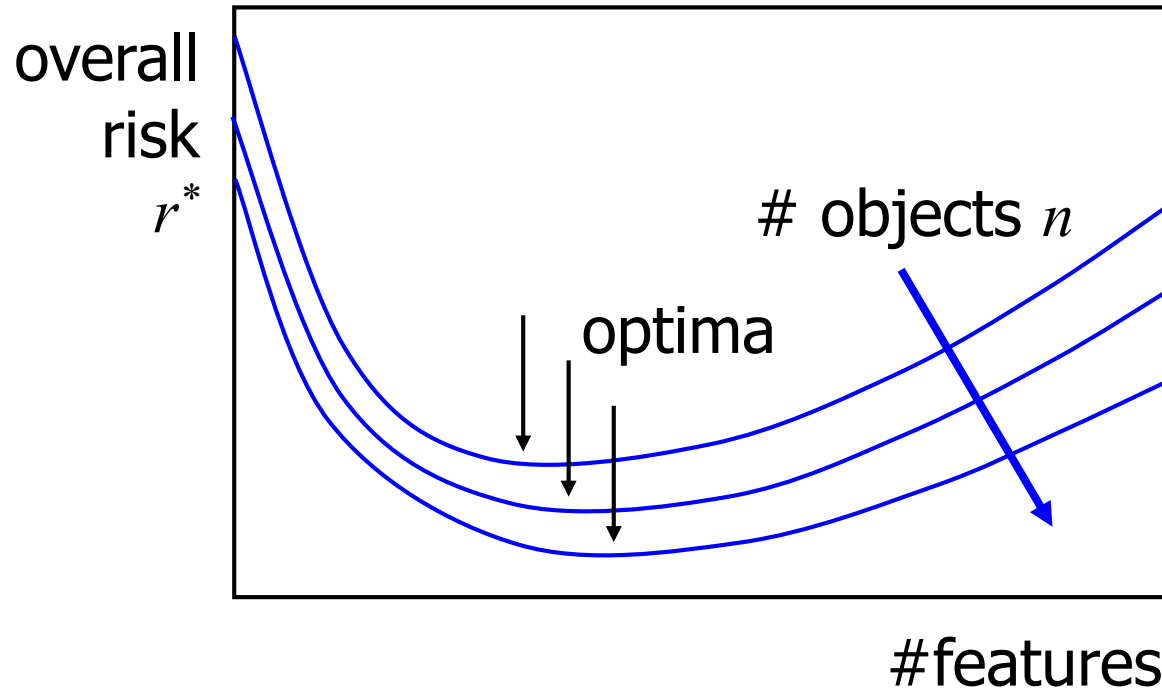


- Unworkable for $p > 2$ measurements

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

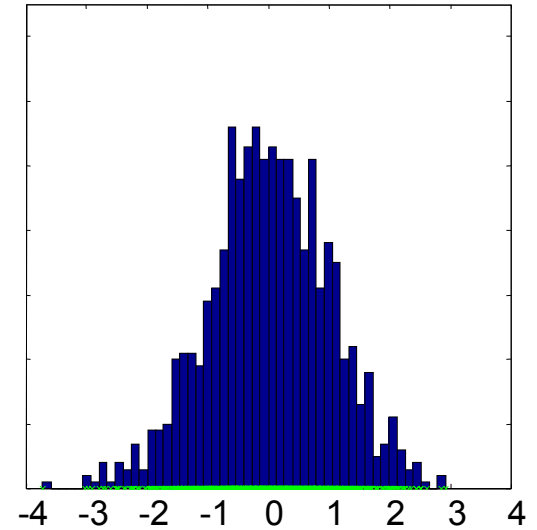
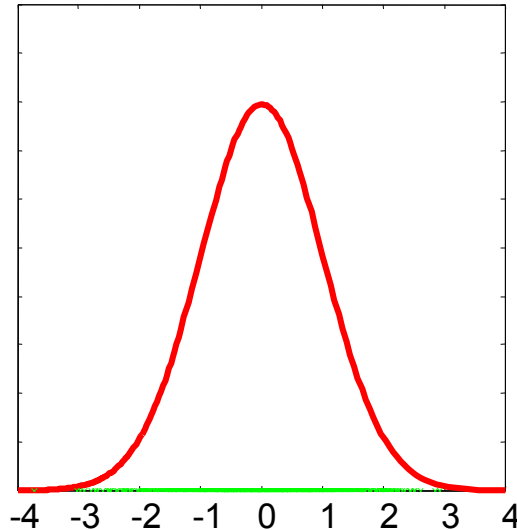
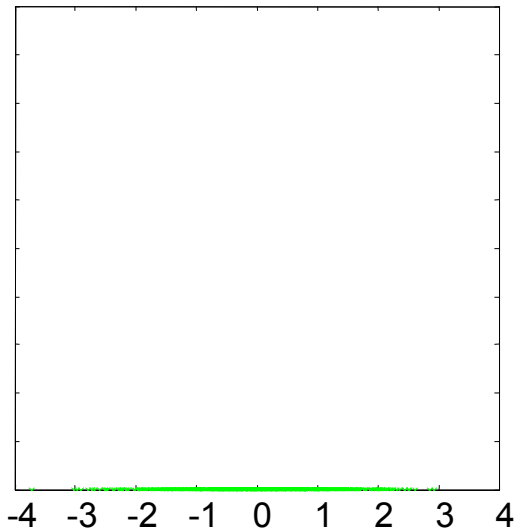
Curse of dimensionality (2)



So, realize if $n \rightarrow \text{INF}$ than you can have many features

Density estimation (4)

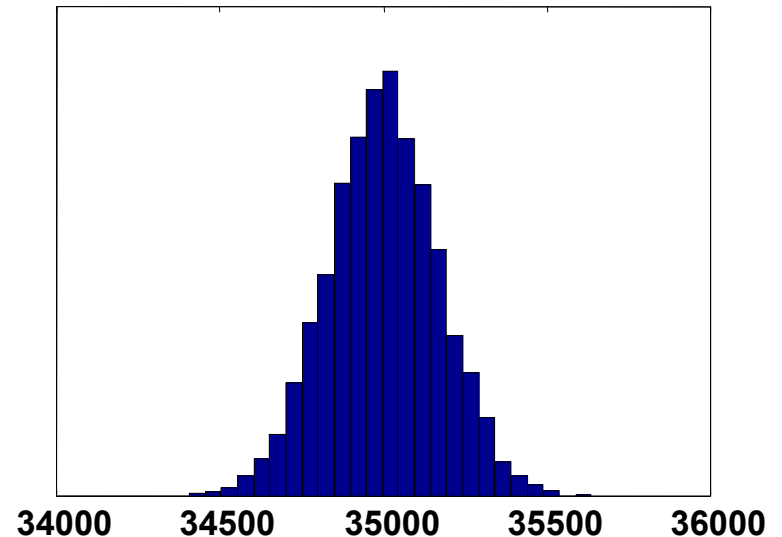
- Two main approaches:
 - *parametric*: assume simple *global* model, e.g. Gaussian, and estimate its parameters
 - *non-parametric*: assume simple *local* model, e.g. uniform, Gaussian, and aggregate



The Gaussian distribution

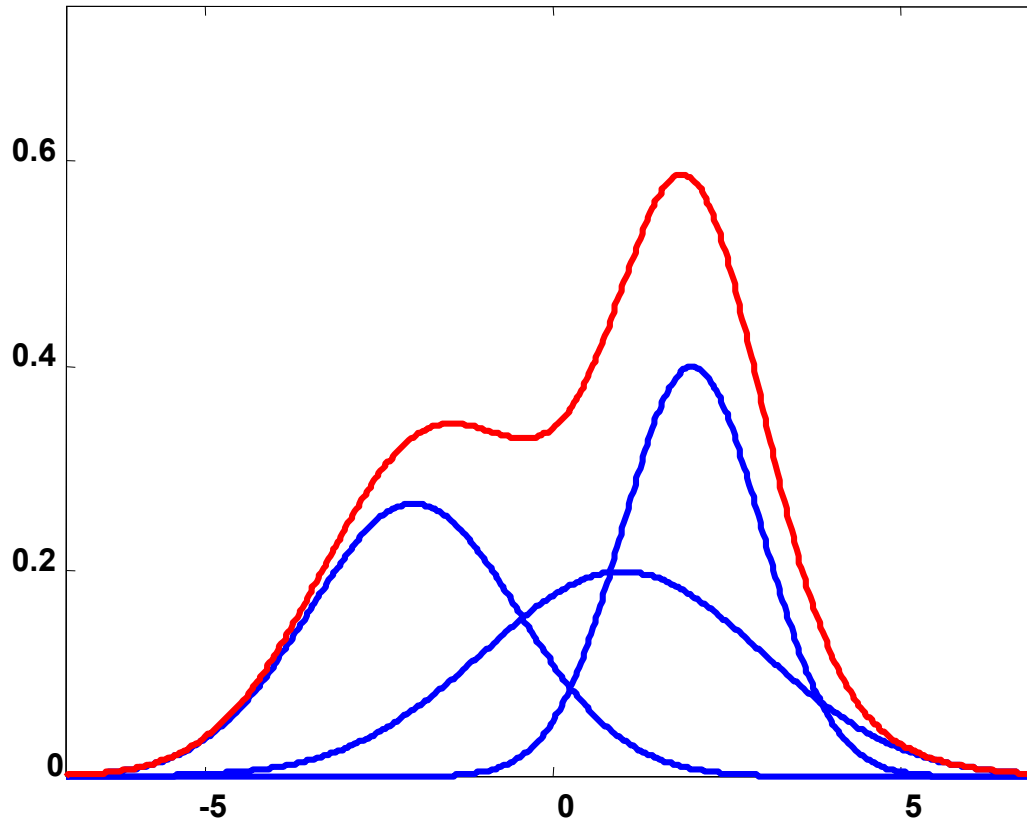
- Why Gaussians?
 - Special distribution: the Central Limit Theorem says that sums of large numbers of i.i.d. (independent, identically distributed) random variables will have a Gaussian distribution
 - Simple, few parameters
 - Often occurs in real life

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



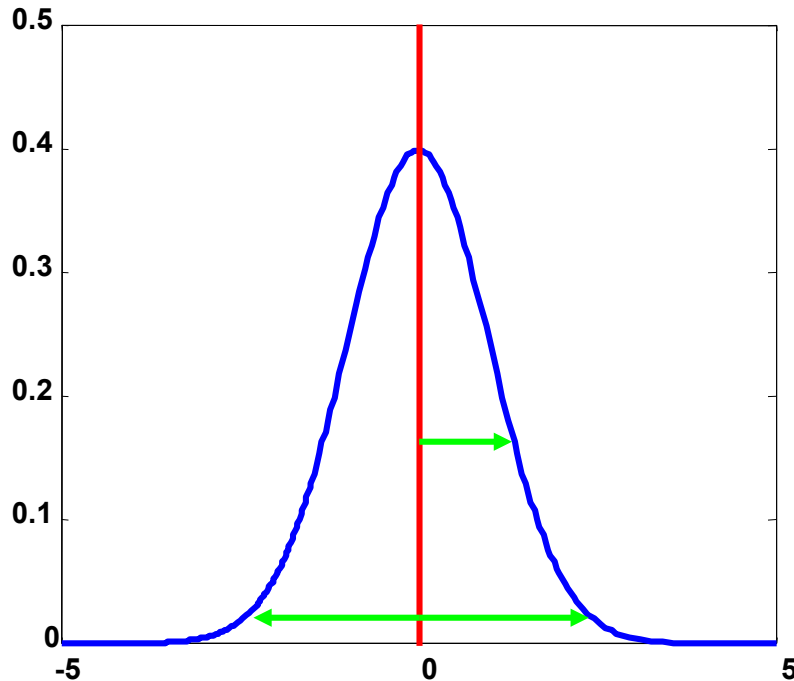
The Gaussian distribution (2)

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



- Gaussian
- Mixture of Gaussians

The Gaussian distribution (3)

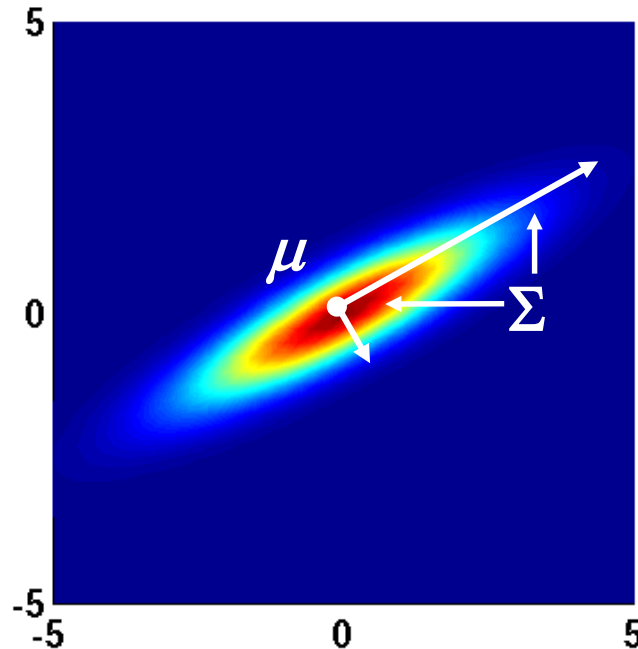


- Normal distribution = Gaussian distribution
- Standard normal distribution:
 $\mu = 0, \sigma^2 = 1$
- 95.45% of data between
 $[\mu - 2\sigma, \mu + 2\sigma]$ (in 1D!)

- 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

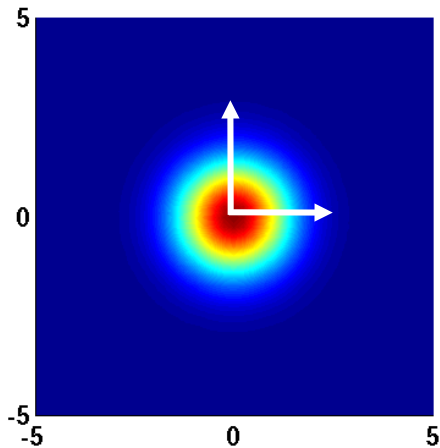


$$\Sigma = \begin{bmatrix} 3 & 1\frac{1}{2} \\ 1\frac{1}{2} & 2 \end{bmatrix}$$

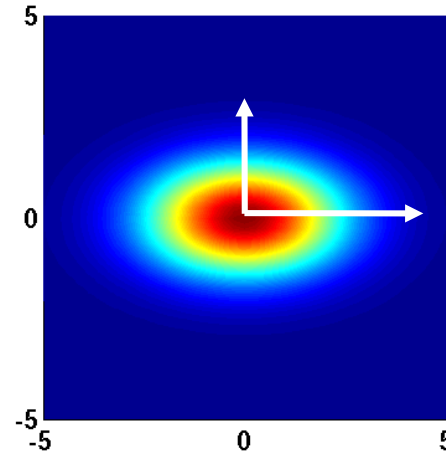
- p - dimensional density:

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

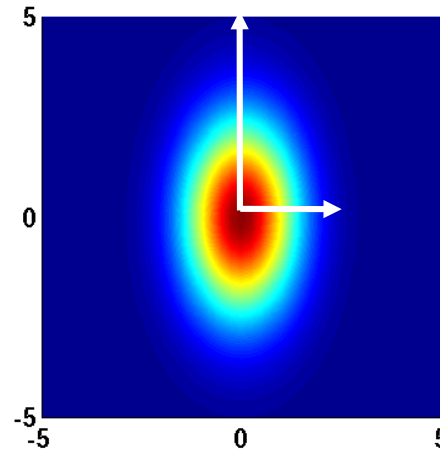
Multivariate Gaussian distribution (2)



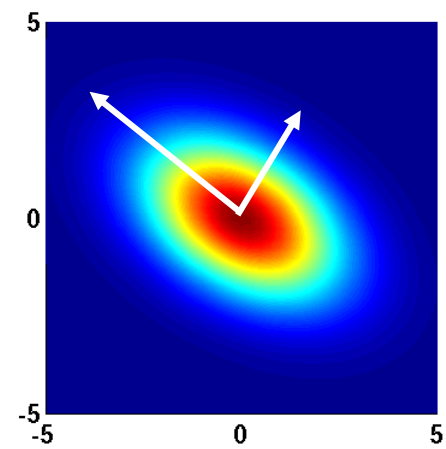
$$\Sigma = \begin{bmatrix} 1 & 0 \\ 0 & 1 \end{bmatrix}$$



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



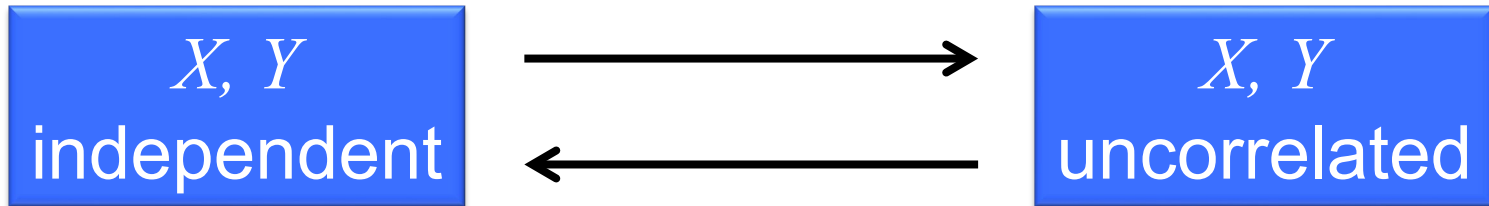
$$\Sigma = \begin{bmatrix} 1 & 0 \\ 0 & 3 \end{bmatrix}$$



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

Special properties

- The Gaussian distribution is a special case:

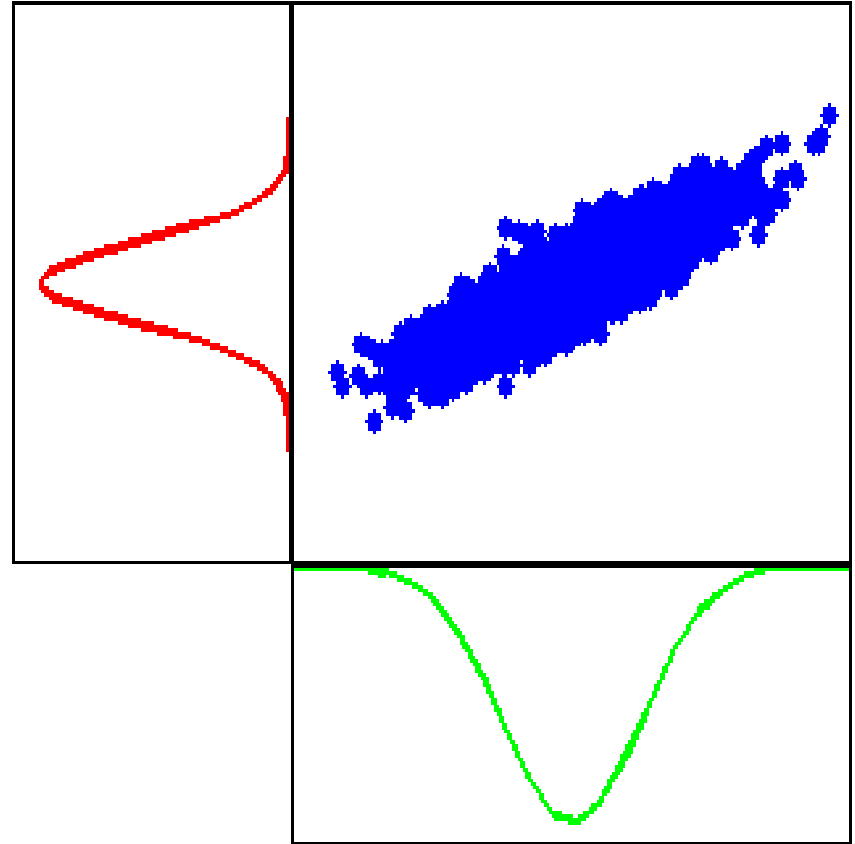


- Proof: if uncorrelated, Σ is diagonal ($\sigma_1 \dots \sigma_p$)

$$\begin{aligned} p(\mathbf{x}) &= \frac{1}{\sqrt{2\pi^p \det(\Sigma)}} \exp\left(-\frac{1}{2}(\mathbf{x} - \boldsymbol{\mu})^\top \Sigma^{-1}(\mathbf{x} - \boldsymbol{\mu})\right) \\ &= \frac{1}{\sqrt{2\pi\sigma_1^2}} \exp\left(-\frac{1}{2}(x_1 - \mu_1)^\top \sigma_1^{-2}(x_1 - \mu_1)\right) \times \frac{1}{\sqrt{2\pi\sigma_2^2}} \exp\left(-\frac{1}{2}(x_2 - \mu_2)^\top \sigma_2^{-2}(x_2 - \mu_2)\right) \\ &\quad \times \dots \times \frac{1}{\sqrt{2\pi\sigma_p^2}} \exp\left(-\frac{1}{2}(x_p - \mu_p)^\top \sigma_p^{-2}(x_p - \mu_p)\right) = p(x_1)p(x_2)\dots p(x_p) \end{aligned}$$

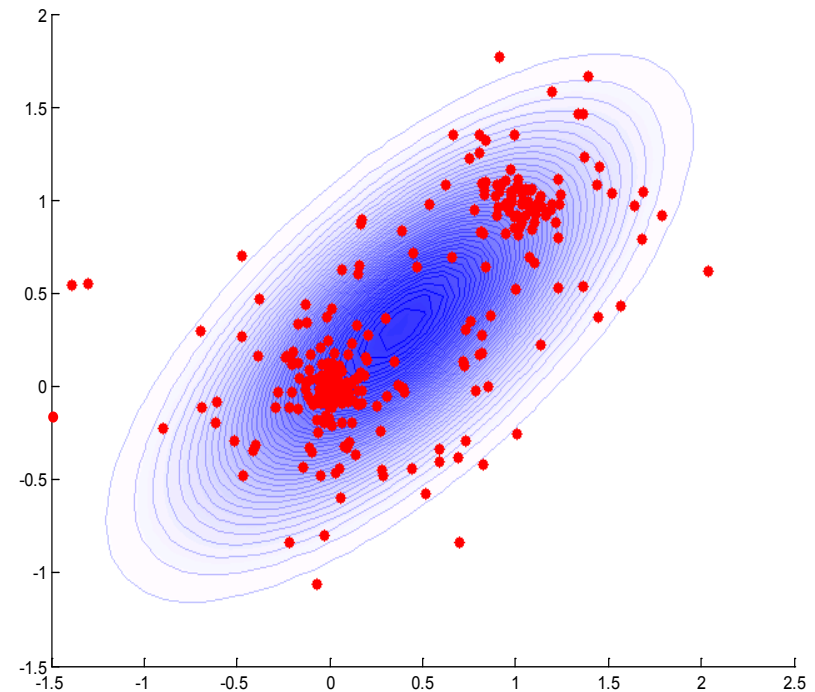
Special properties (2)

- 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

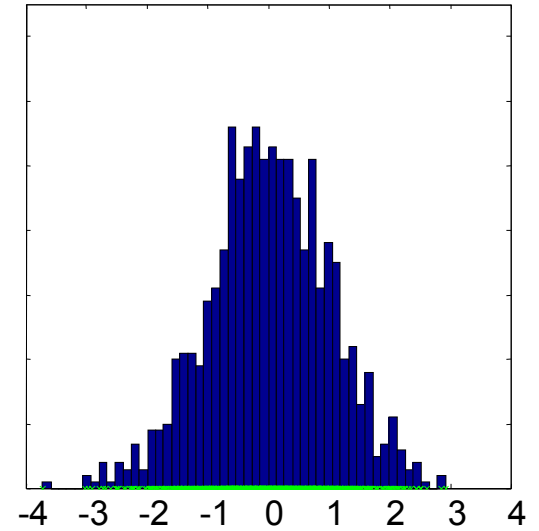
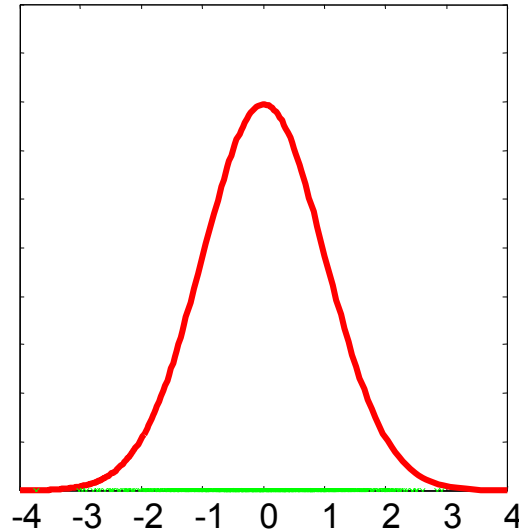
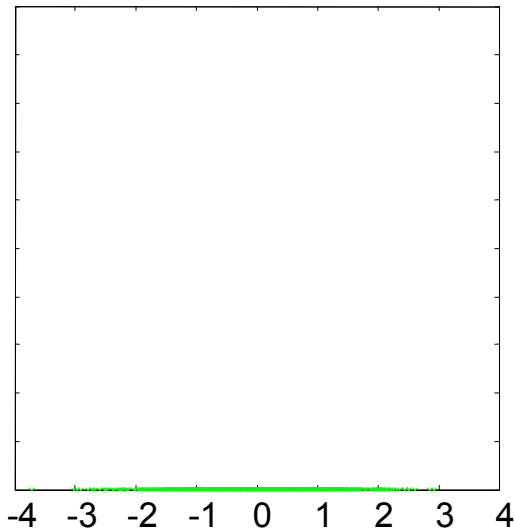




10min break

Density estimation (4)

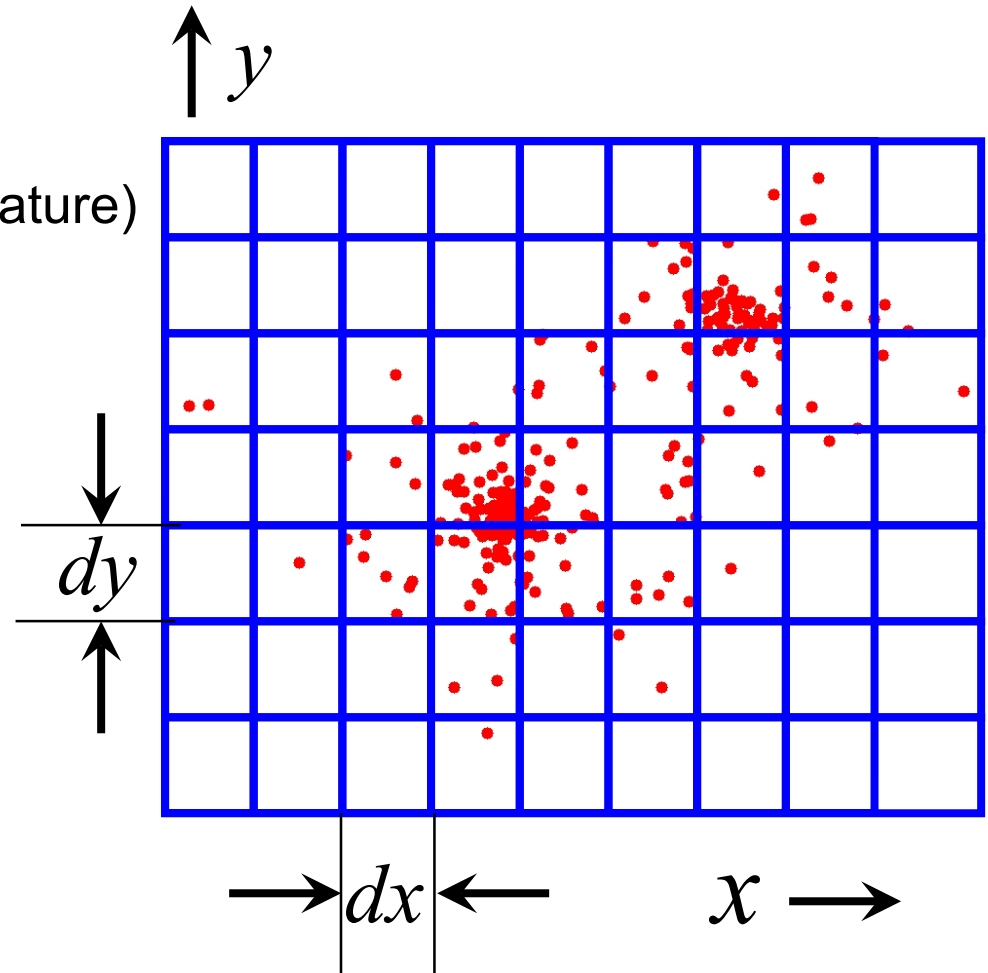
- Two main approaches:
 - *parametric*: assume simple *global* model, e.g. Gaussian, and estimate its parameters
 - *non-parametric*: assume simple *local* model, e.g. uniform, Gaussian, and aggregate



Histogramming

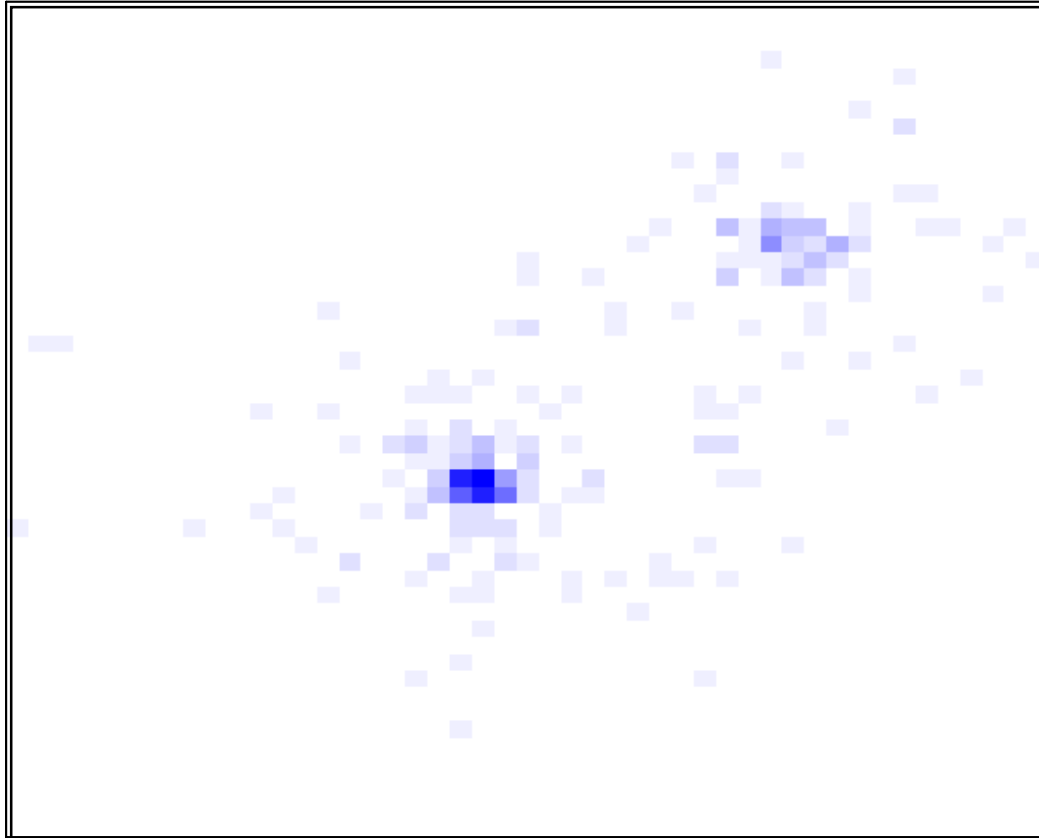
- Histogram method:
 - Divide feature space into N^p bins (N bins per feature)
 - Count number of objects in each bin
 - Normalize:

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



Histogramming (2)

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

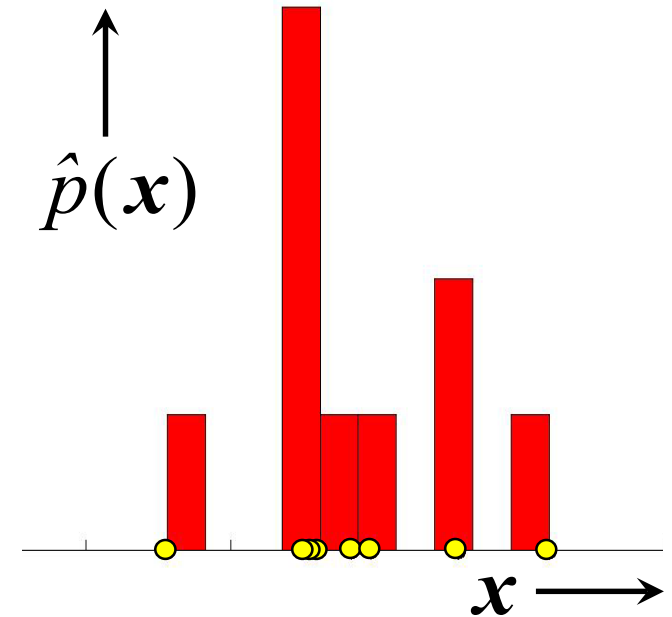


Histogramming (3)

- Histogram density estimate:

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

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

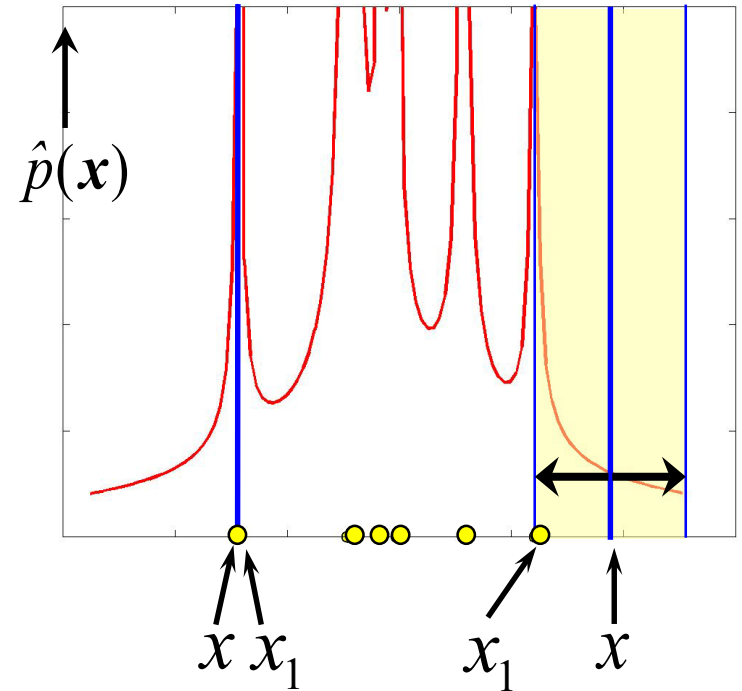


k-nearest neighbor density estimation

- k-nearest neighbor estimate:

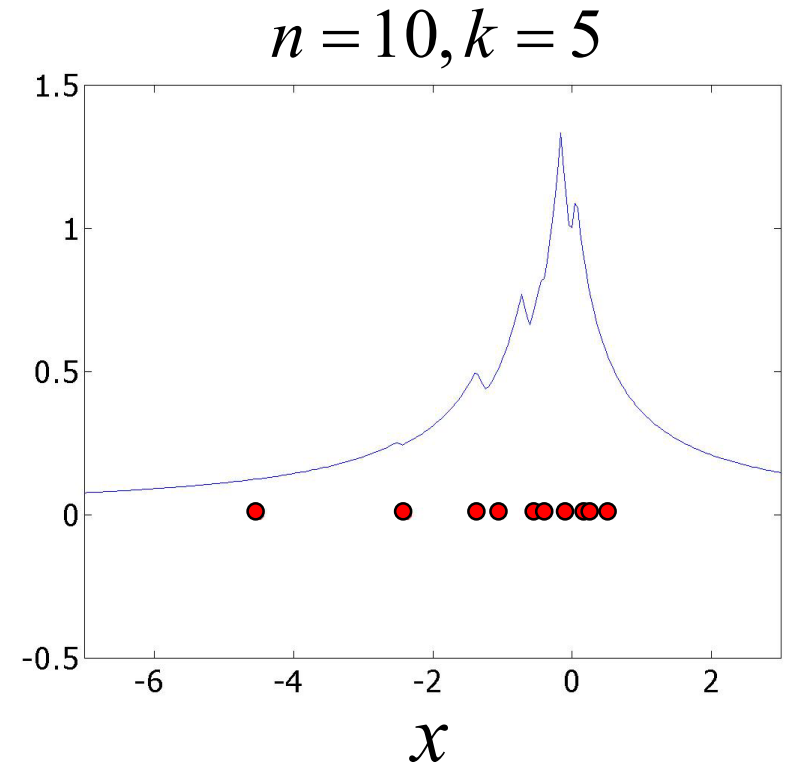
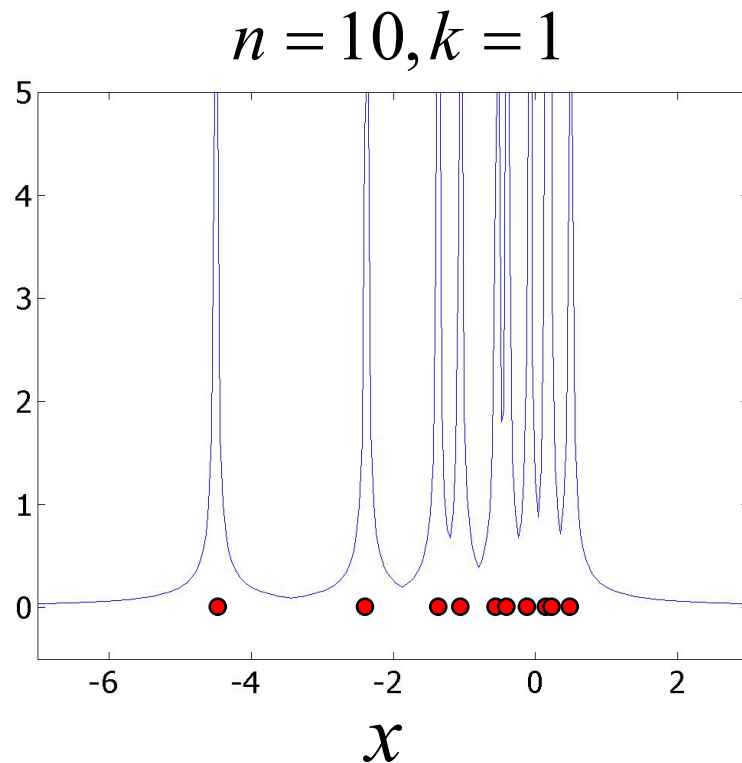
$$\hat{p}(x | k) = \left(\frac{\text{fraction of objects}}{\text{volume}} \right) \hat{p}(x)$$
$$= \frac{k}{n \Delta x_k} = \frac{k}{n \|x - x_k\|}$$

- 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

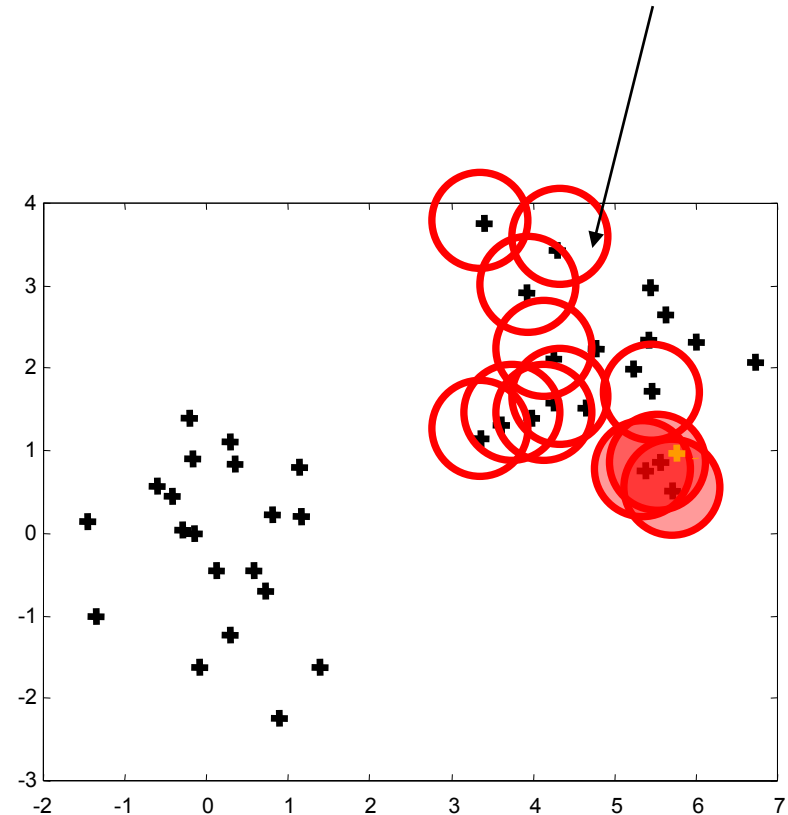
- Procedure:
 - Fix volume of cell
 - Vary positions of cells
 - Add contributions of cells
- Define cell shape (kernel), e.g. uniform

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

(with V the volume of the kernel)

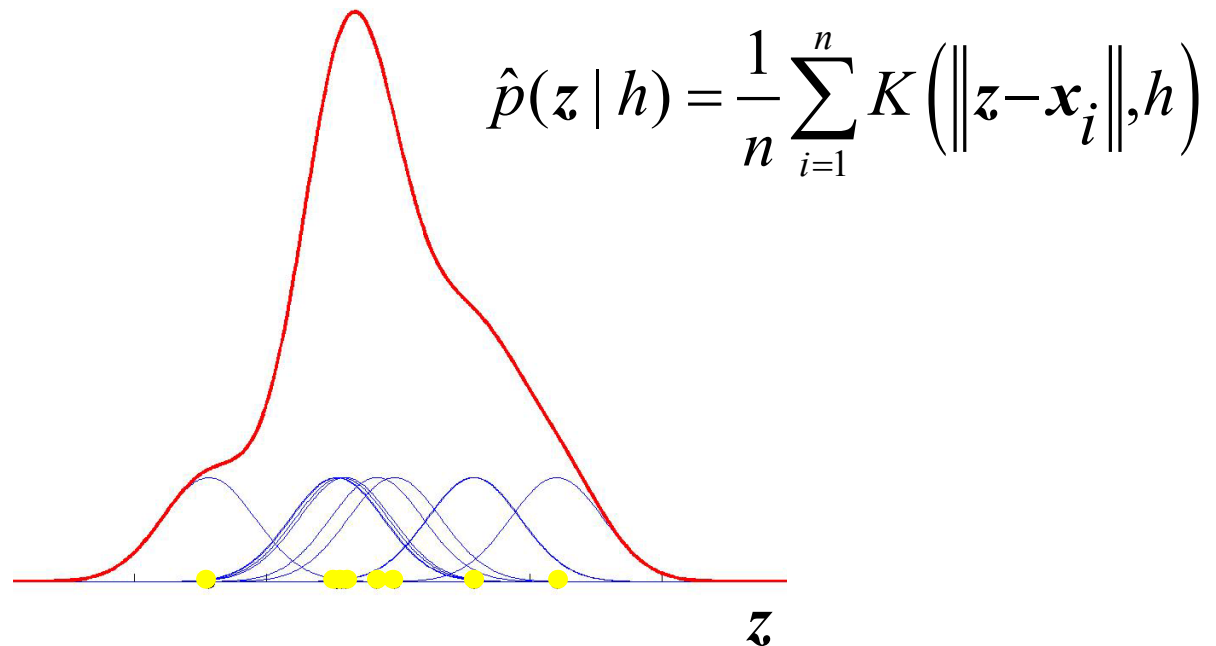
or Gaussian

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



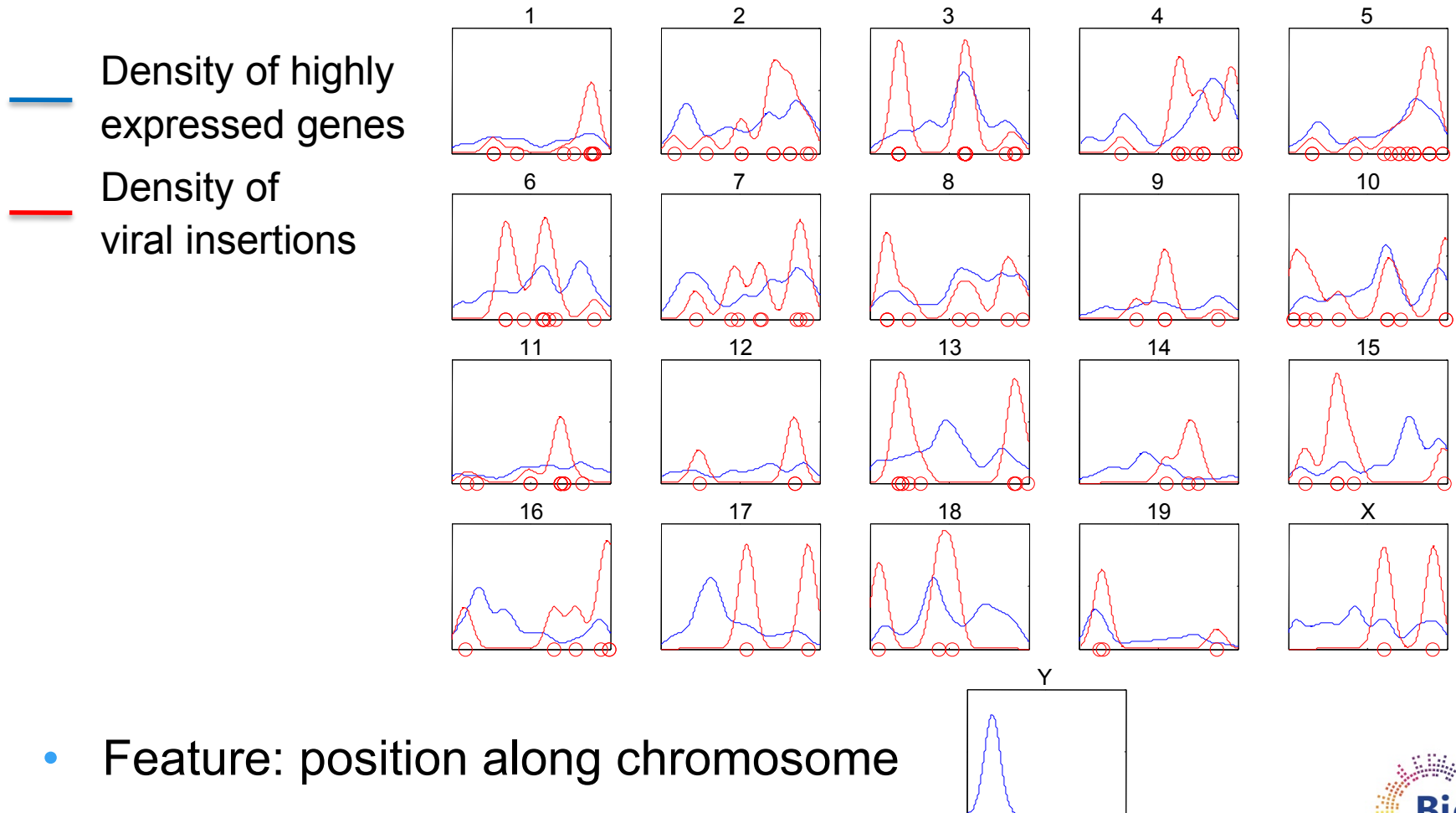
Parzen density estimation (2)

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



Parzen density estimation (3)

- Example: viral insertions in each chromosome



- 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 z :

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

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

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

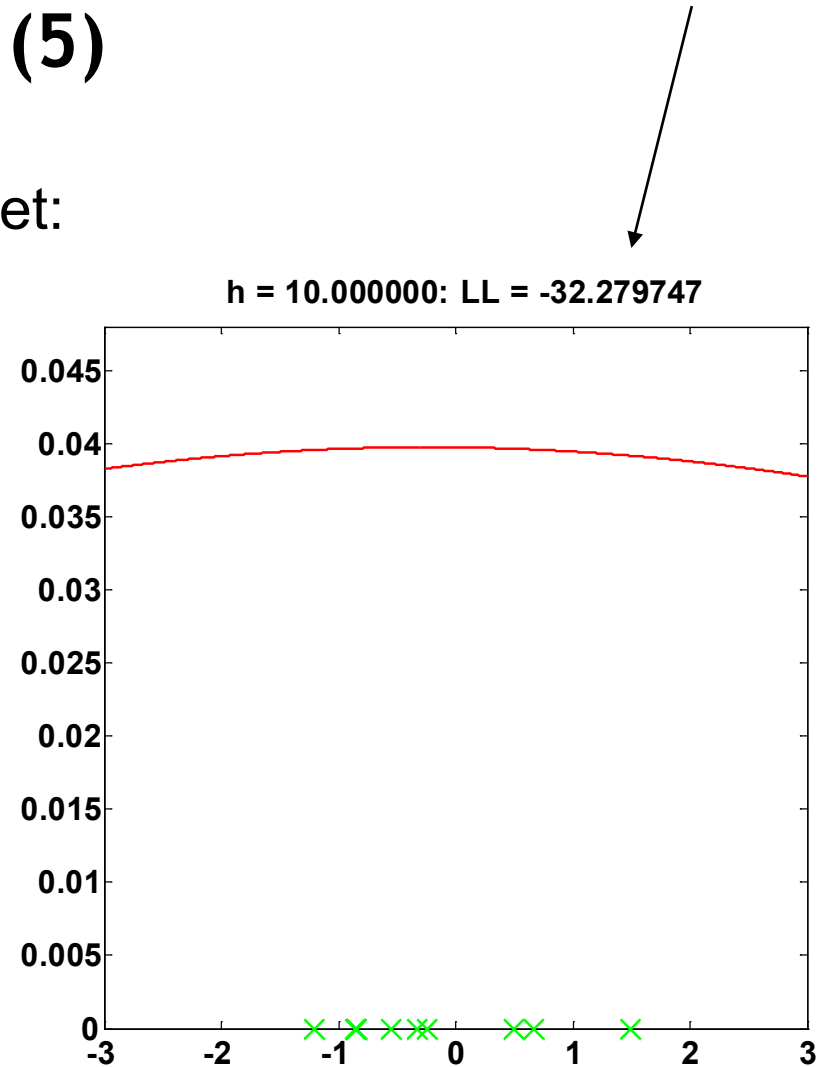
(this assumes independence!)

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

$$LL = \log(g(\mathbf{x}_1, \dots, \mathbf{x}_n)) = \sum_{i=1}^n \log(\hat{p}(\mathbf{x}_i | h))$$

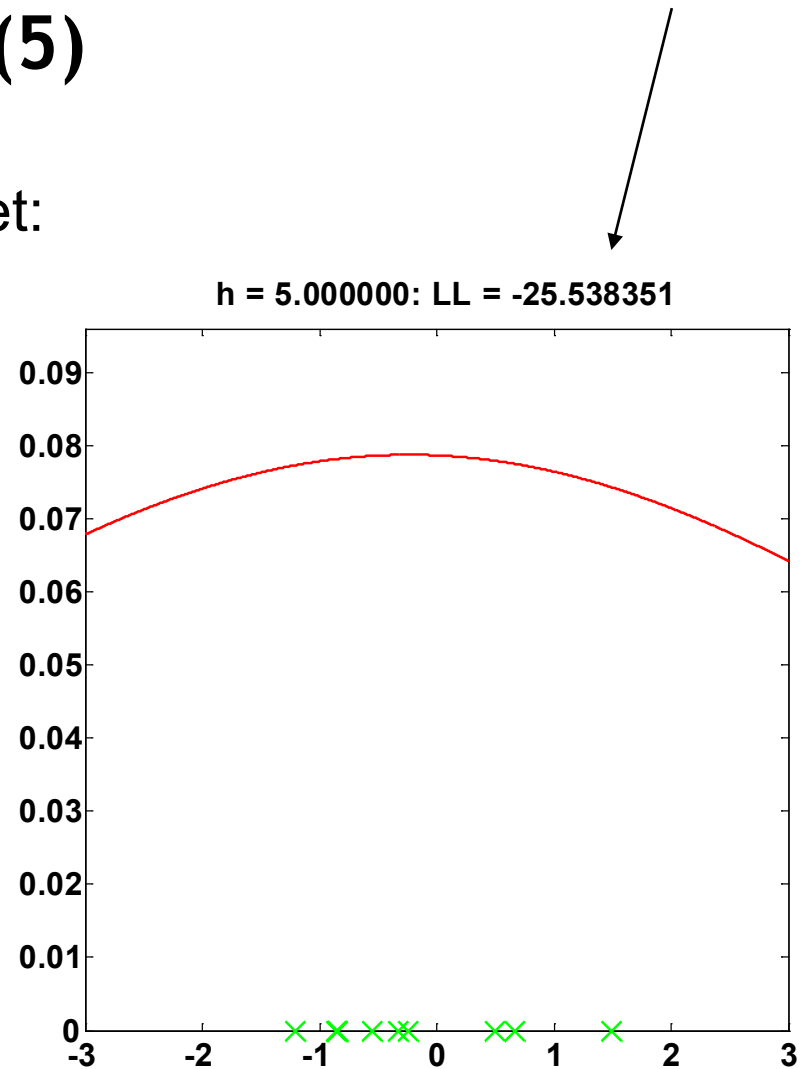
Parzen density estimation (5)

- Maximum likelihood on training set:



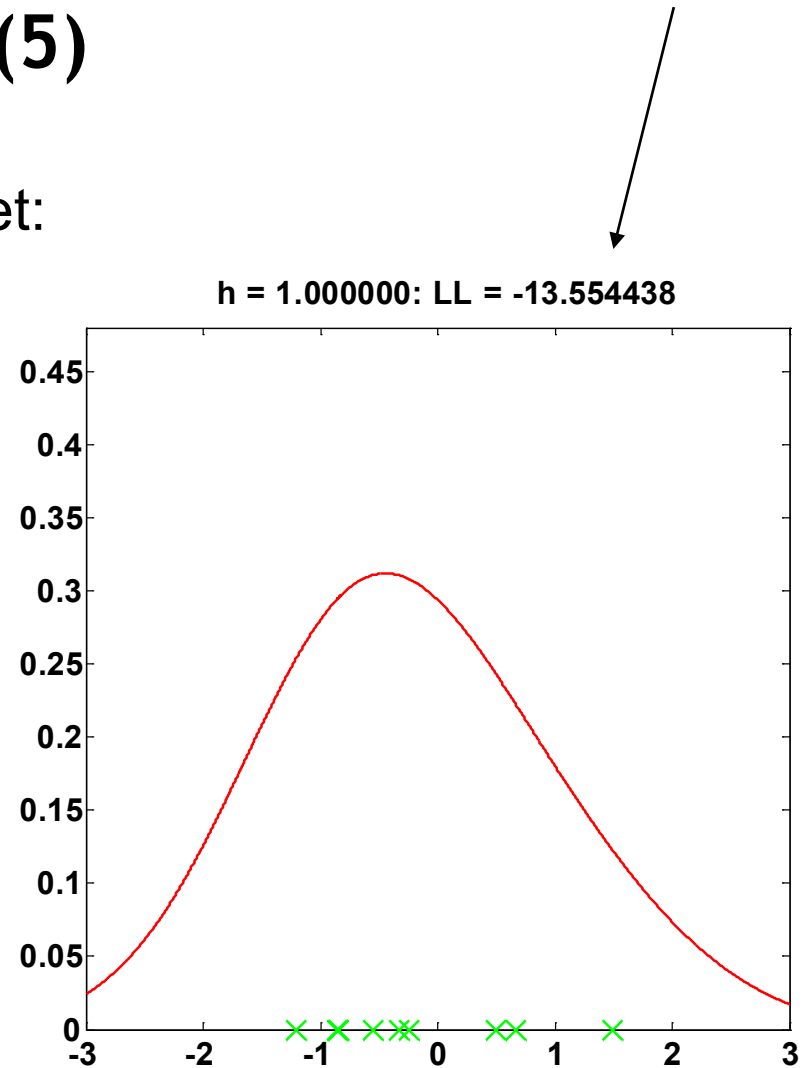
Parzen density estimation (5)

- Maximum likelihood on training set:



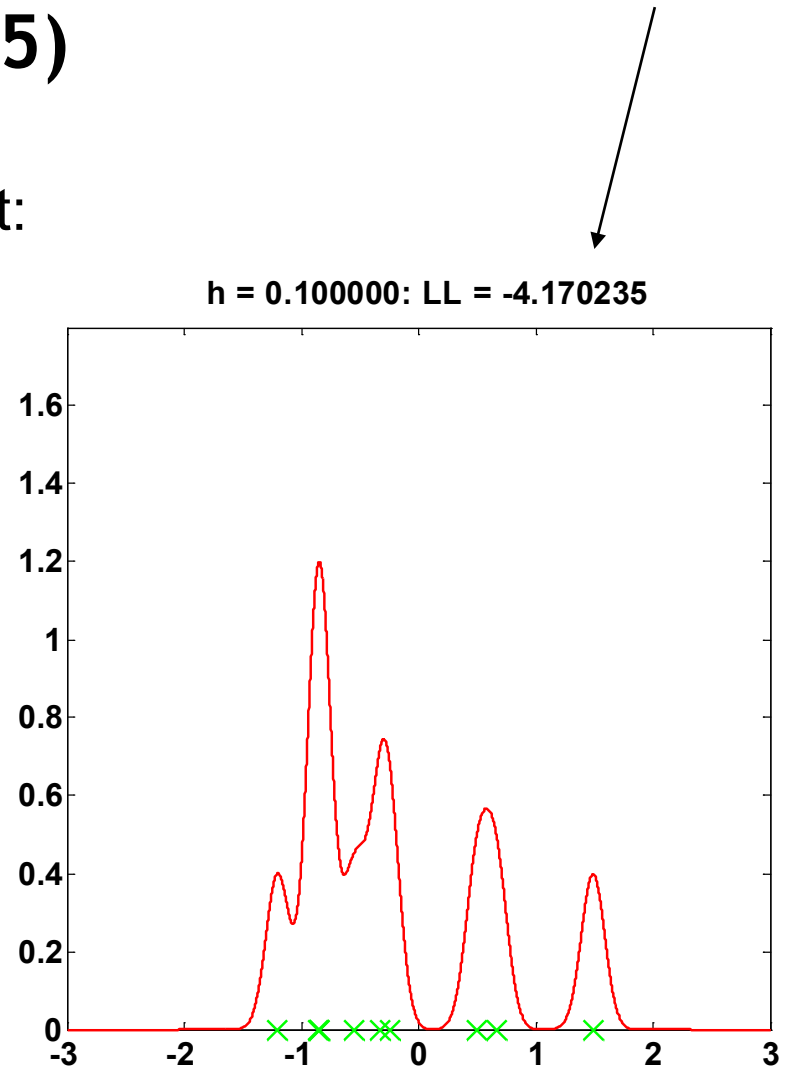
Parzen density estimation (5)

- Maximum likelihood on training set:



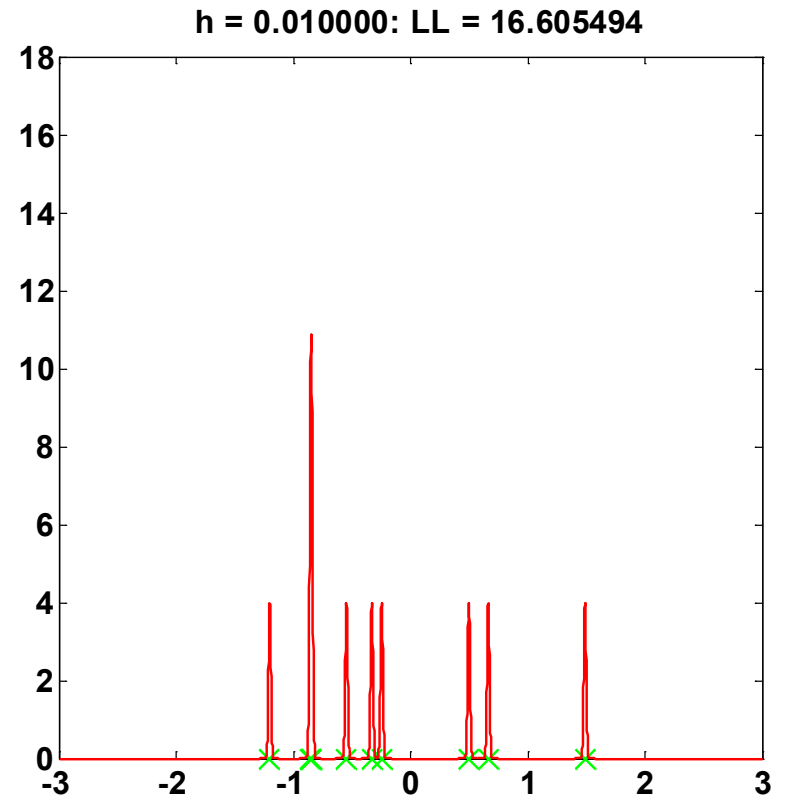
Parzen density estimation (5)

- Maximum likelihood on training set:



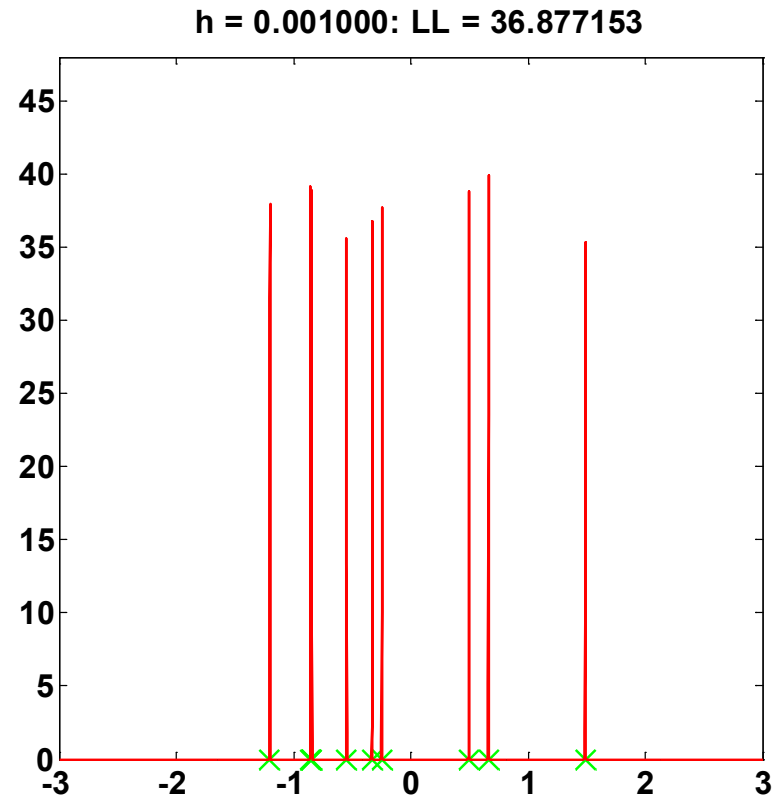
Parzen density estimation (5)

- Maximum likelihood on training set:



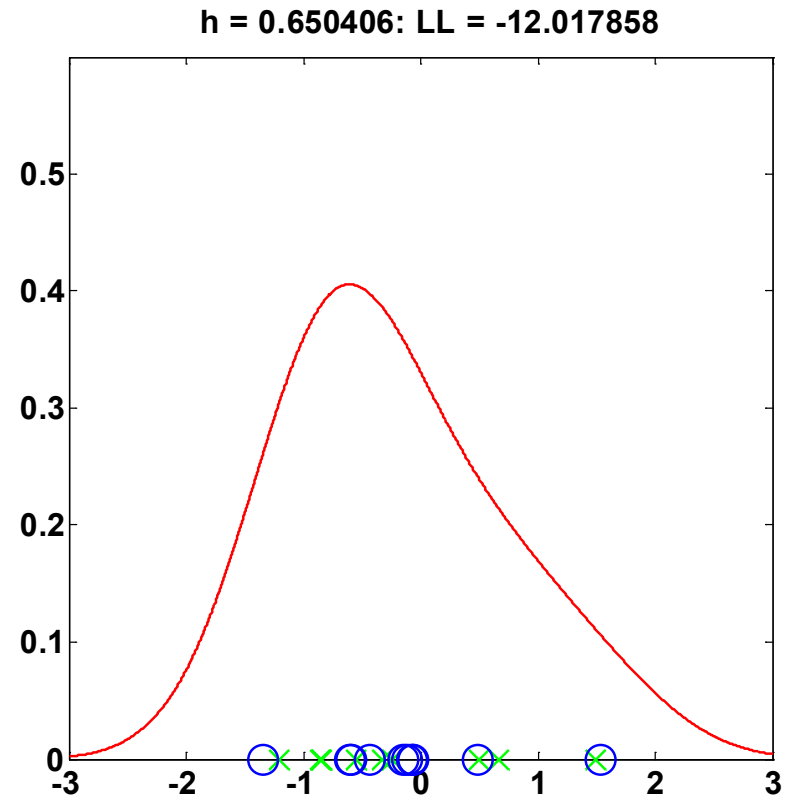
Parzen density estimation (5)

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



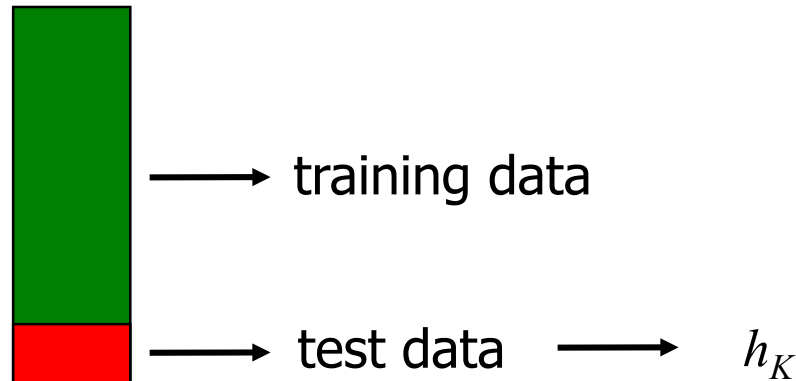
Cross-validation

- 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



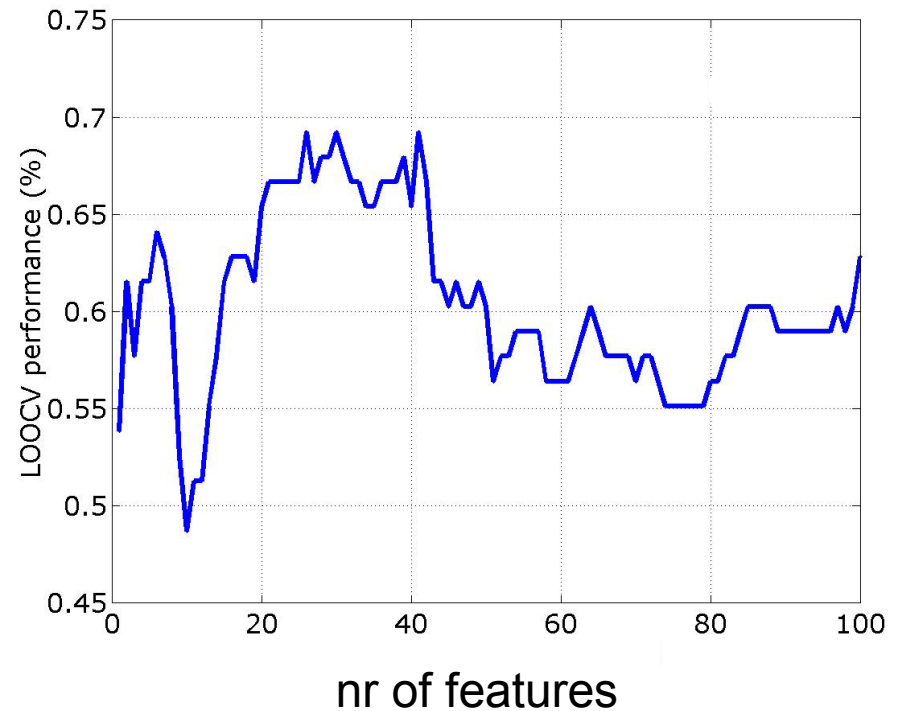
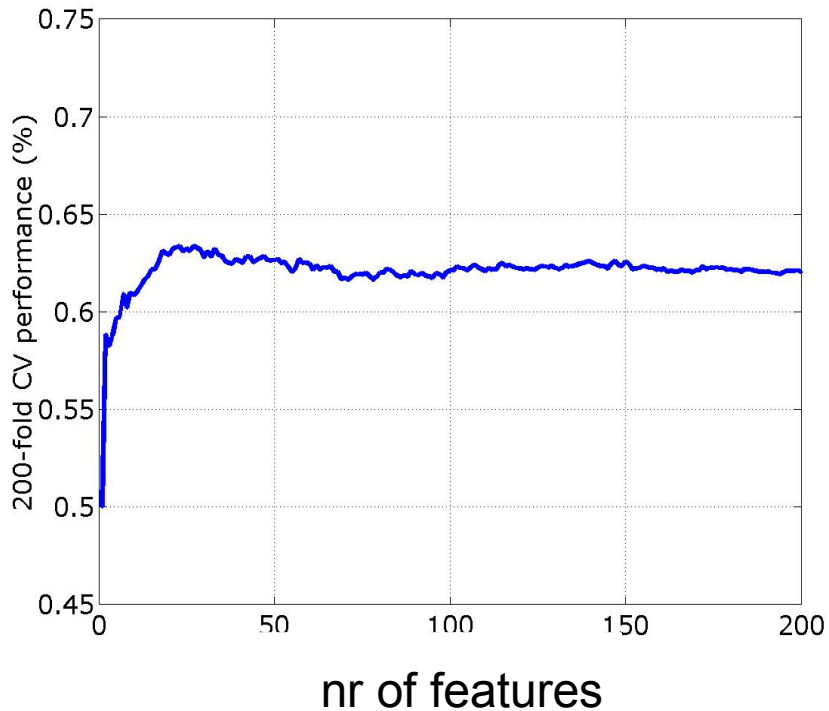
Cross-validation (2)

- 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



Cross-validation (3)

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



Bootstrap

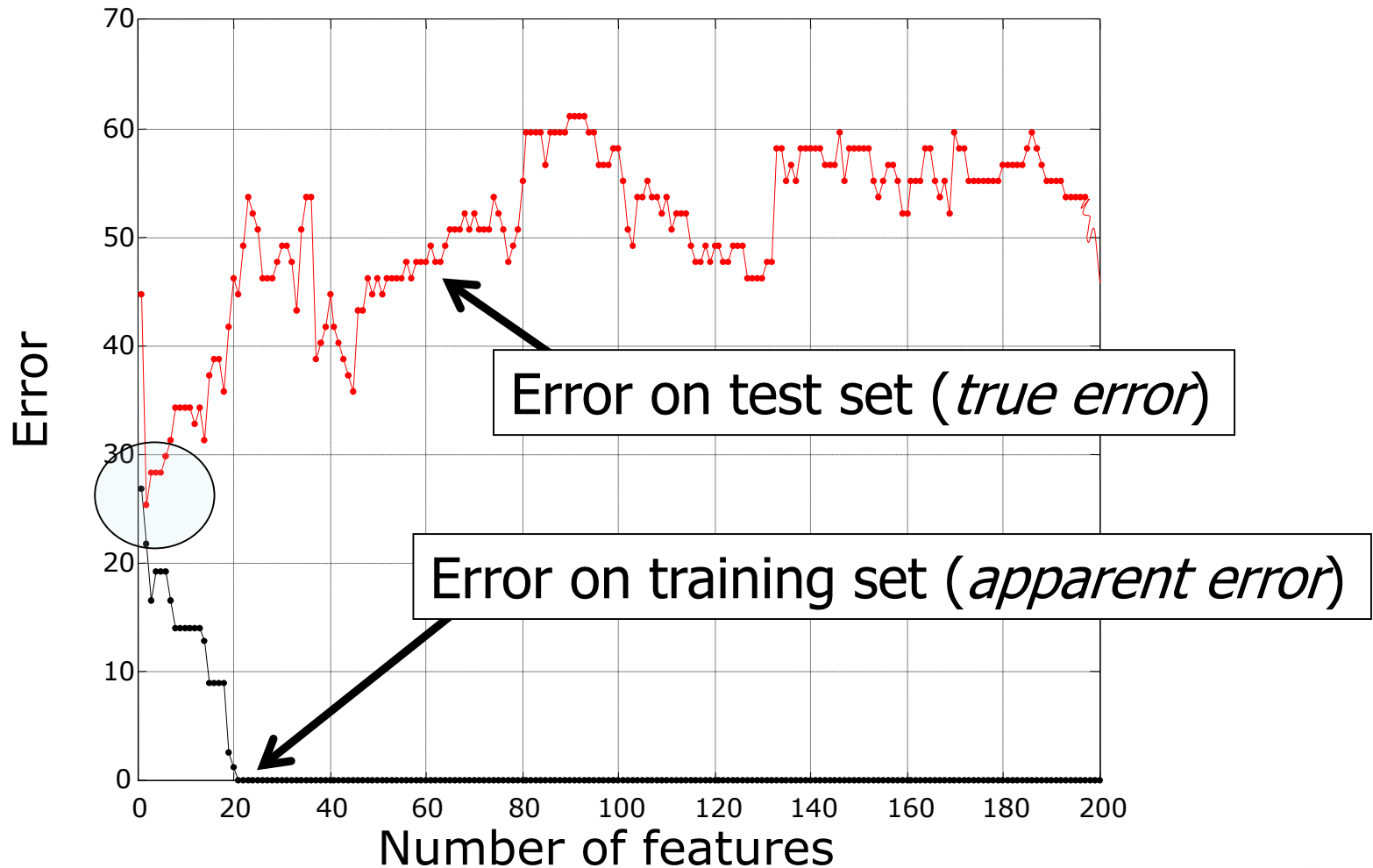
- Alternative to cross-validation:
 - Repeat K times:
 - Draw n objects from the dataset, **with replacement** (some objects will be selected more than once)
 - Test using objects that were not selected
- Cross-validation and bootstrap estimates are *biased*
 - They are conservative (i.e. too pessimistic) 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

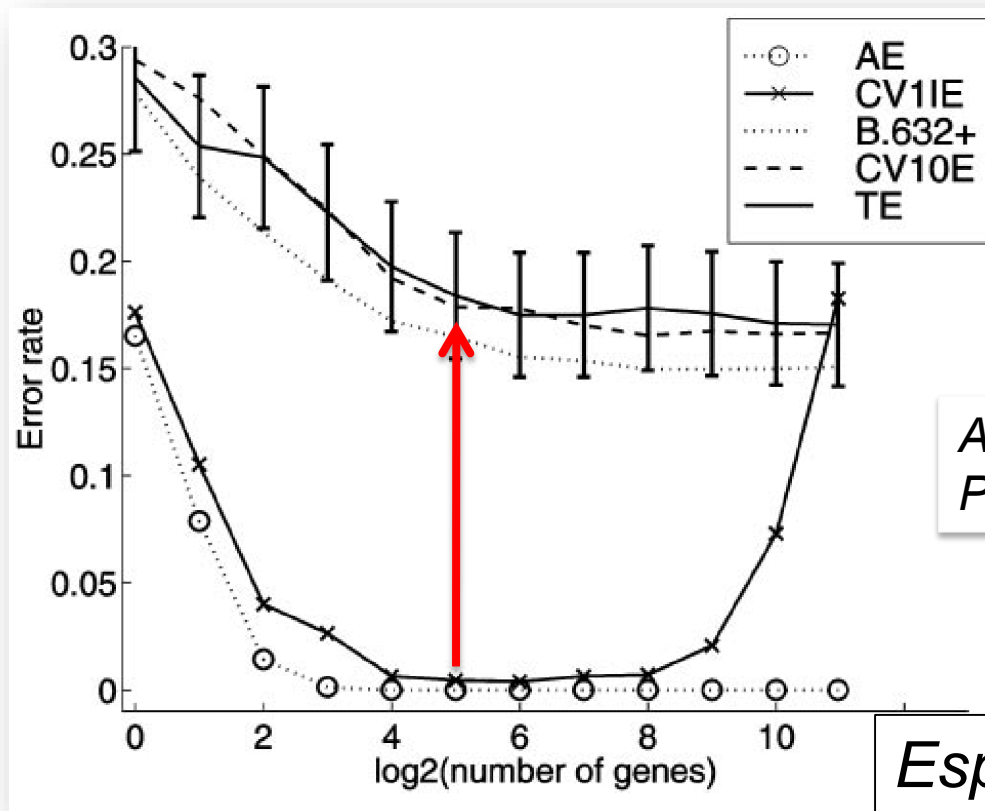
- Terminology:
 - A *training set* is used to estimate parameters
 - An optional *validation set* is used to optimize parameter settings, e.g. by calculating classifier error on this set
 - **A *test set* is only used to judge performance of the entire classifier (only used once!)**
- Error estimates: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

Training, test and validation sets (2)



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



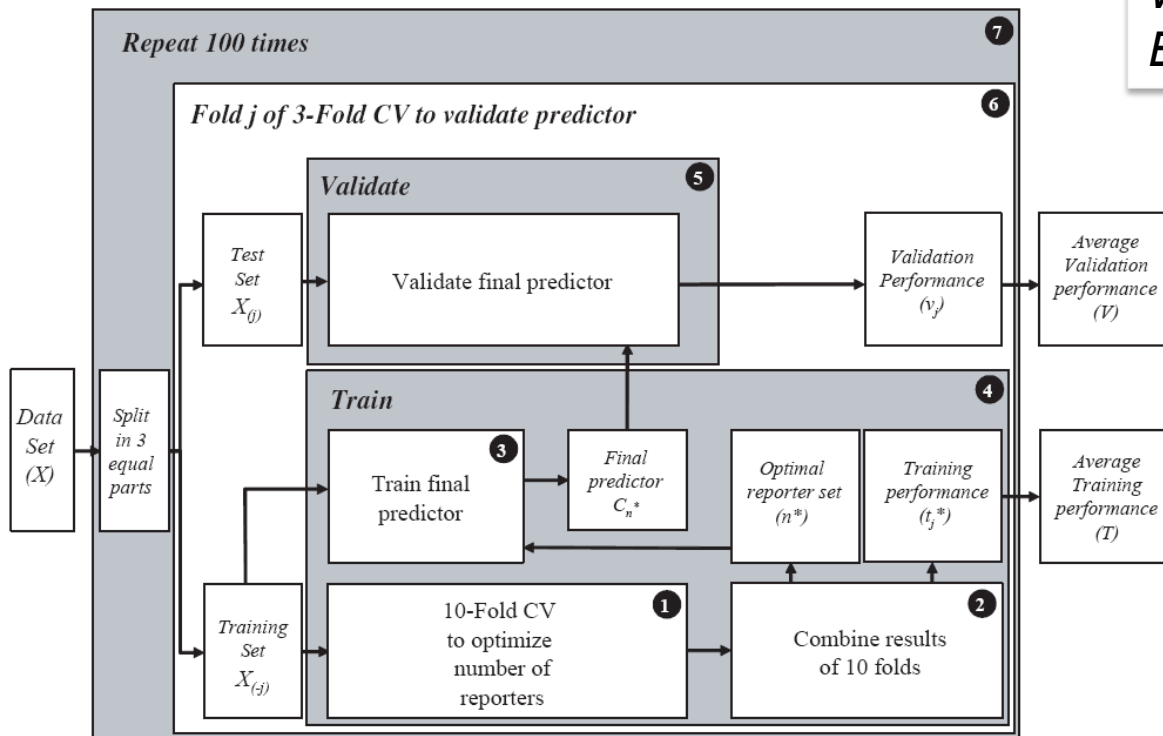
*Ambroise et al.,
PNAS 2002*

*Especially in bioinformatics
i.e. $p \gg n$ 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